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      S2    5801  S1 AND DIFFERENT?
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          482795  VIRAL?
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 6/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13521353   22193520   PMID: 12205638
  Cell transplantation for stroke.
  Savitz Sean I; Rosenbaum Daniel M; Dinsmore Jonathan H; Wechsler Lawrence
R; Caplan Louis R
  Department of Neurology, Beth Israel Deaconess Medical Center and Harvard
Medical School, Boston, MA.
  Annals of neurology (United States)  Sep 2002,  52  (3)  p266-75,  ISSN
0364-5134   Journal Code: 7707449
  Document type: Journal Article
  Languages: ENGLISH
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Main Citation Owner: NLM
Record type: In Process
Cell transplantation has emerged as an experimental approach to restore brain function after stroke. Various **cell** types including porcine fetal **cells**, stem **cells**, **immortalized cell** lines, and marrow stromal **cells** are under investigation in experimental and clinical stroke trials. This **review** discusses the unique advantages and limitations of the **different** graft sources and emphasizes the current, limited knowledge about their biology. The survival, integration, and efficacy of neural transplants in stroke patients will depend on the type, severity, chronicity, adequacy of circulation, and location of the stroke lesion. Ann Neurol 2002;52:266-275

6/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13494021 22161263 PMID: 12170780
Id proteins--tumor markers or oncogenes?
Hasskarl Jens; Munger Karl
Department of Pathology, Harvard Center for Cancer Biology, Harvard Medical School, 200 Longwood Avenue, Building D2, Room 544A, Boston, Massachusetts 02115-5701, USA.
Cancer Biol Ther (United States) Mar-Apr 2002, 1 (2) p91-6, ISSN 1538-4047 Journal Code: 101137842
Contract/Grant No.: P01 DE00275; DE; NIDCR; R01 CA66980; CA; NCI; R01 CA81135; CA; NCI
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The Id (Inhibitor of **differentiation** or Inhibitor of DNA-binding) proteins act as dominant negative inhibitors of **differentiation** -specific basic Helix-Loop-Helix (bHLH) transcription factors. Id proteins negatively regulate **cellular differentiation** and they induce proliferation by modulating **different cell** cycle regulators both by direct and indirect mechanisms. Ectopic expression of Id proteins in tissue culture models can result in **cellular immortalization** and abrogation of **differentiation** processes. Recent reports show that Id proteins are overexpressed in various cancer types implying a role of these regulatory proteins in carcinogenesis. This **review** focuses on the biology of the Id proteins and their role as potential oncogenes.

6/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13354510 22029638 PMID: 12033726
Derivation and spontaneous **differentiation** of human embryonic stem **cells**.
Amit Michal; Itskovitz-Eldor Joseph
Department of Obstetrics and Gynecology, Rambam Medical Center, Haifa, Israel.
Journal of anatomy (England) Mar 2002, 200 (Pt 3) p225-32, ISSN 0021-8782 Journal Code: 0137162
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Embryonic stem (ES) **cells** are unique **cells** derived from the inner **cell** mass of the mammalian blastocyst. These **cells** are **immortal** and pluripotent, retain their developmental potential after prolonged culture, and can be continuously cultured in an undifferentiated state. Many in vitro **differentiation** systems have been developed for

mouse ES **cells**, including reproducible methods for mouse ES **cell differentiation** into haematopoietic and neural precursors, cardiomyocytes, insulin-secreting **cells**, endothelial **cells** and various other **cell** types. The derivation of new human ES **cell** lines provides the opportunity to develop unique models for developmental research and for **cell** therapies. In this **review** we consider the derivation and spontaneous **differentiation** of human ES **cells**.

6/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13296250 22074890 PMID: 12079483
Spontaneous regression of neoplasms: new possibilities for immunotherapy.
Bodey Bela
University of Southern California, 8000-1 Canby Avenue, Reseda, CA 91335, USA. Bodey18@aol.com
Expert Opin Biol Ther (England) Jun 2002, 2 (5) p459-76, ISSN 1471-2598 Journal Code: 101125414
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
In mammalian **cells** , neoplastic transformation is directly associated with the expression of oncogenes, loss or simple inactivation of the function of tumour suppressor genes and the production of certain growth factors. Genes for suppression of the development of the neoplastic **cellular** immunophenotype, as well as inhibitory growth factors, have regulatory functions within the normal processes of **cell** division and **differentiation** . Telomerase (a ribonucleoprotein polymerase) activation is frequently detected in various neoplasms. Telomerase activation is regarded as essential for **cell immortalisation** and its inhibition may result in spontaneous regression of neoplasms. This phenomenon of neoplasms occurs when the malignant tissue mass partially or completely disappears without any treatment or as a result of a therapy considered inadequate to influence systemic neoplastic growth. This definition makes it clear that the term 'spontaneous regression' applies to neoplasms in which the overall malignant disease is not necessarily cured and to cases where the regression may not be complete or permanent. A number of possible mechanisms of spontaneous regression are **reviewed**, with the understanding that no single mechanism can completely account for this phenomenon. The application of the newest immunological, molecular biological and genetic insights for more individualised and adequate antineoplastic immunotherapy (alternative biotherapy) is also discussed.

6/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13224541 21998114 PMID: 12003383
Telomerase activity in pancreatic endocrine tumors.
Tang Shou-Jiang; Dumot John A; Wang Liming; Memmesheimer Christian; Conwell Darwin L; Zuccaro Gregory; Goormastic Marlene; Ormsby Adrian H; Cowell John
Department of Medicine, Cleveland Clinic Foundation, Ohio 44195, USA.
American journal of gastroenterology (United States) Apr 2002, 97 (4) p1022-30, ISSN 0002-9270 Journal Code: 0421030
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
OBJECTIVES: Pancreatic endocrine tumors (PETs) have variable prognoses, and predictors of survival are lacking. PETs can be difficult to distinguish histologically from aggressive pancreatic neoplasms such as

acinar **cell** carcinoma. Telomerase is a ribonuclear protein that maintains the length of the telomere and induces **cell immortality** . Telomerase is present in 95% of pancreatic adenocarcinoma and is associated with aggressive tumor behavior. Our aim is to determine telomerase activity in PETs and investigate its potential role as a prognostic indicator. METHODS: Telomerase detection using the telomeric repeat amplification protocol was performed on frozen surgical archived pancreatic endocrine tissue from 30 patients with PETs identified by light microscopy (hematoxylin-eosin stain). All results were confirmed with internal controls. A patient's survival was measured from the time of surgery. Acinar **cell differentiation** (presence of zymogen granules) was determined by electron microscopy. Follow-up data were acquired via telephone interview, medical record **review**, and death certificates. RESULTS: Three of 30 PETs diagnosed by light microscopy were telomerase positive: three were considered nonfunctional, and two of these three patients had extrapancreatic disease. All three telomerase-positive cases were reclassified as either acinar **cell** carcinoma (two cases) or mixed acinar-endocrine **cell** carcinoma (one case). All three patients (mean age = 63 yr) died from tumor progression within 2 yr of surgery (mean = 1.6 yr +/- 0.5 SD). The remaining PETs were telomerase negative: 13 insulinomas, four nonfunctional, two sporadic glucagonomas, one gastrinoma, one vipoma, one carcinoidlike PET, and five PETs from three patients with multiple endocrine neoplasm syndrome type I and two patients with von Hippel-Lindau syndrome. Excluding insulinomas, 12 of 14 patients with telomerase-negative PETs had extrapancreatic disease. Nevertheless, Kaplan-Meier survival estimates for these 12 patients were significantly longer than for patients with telomerase-positive acinar **cell** carcinoma (92% vs 0% at 2 yr, p = 0.001, log rank test). The survival of all telomerase-negative PETs (n = 27) was significantly longer than that of the patients with telomerase-positive acinar **cell** carcinoma (93% vs 0% at 2 yr, p = 0.0001). CONCLUSIONS: Telomerase activity helps to identify acinar **cell** carcinomas that histologically resemble PETs, which accounts for the poor prognosis demonstrated in these patients. The absence of telomerase activity in most PETs may be responsible for their indolent clinical course. Telomerase may identify potentially progressive tumors, such as acinar **cell** carcinoma, and may be useful in selecting patients for more aggressive treatment.

6/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13169793 22009005 PMID: 12014828
Signaling on telomerase: a master switch in **cell** aging and **immortalization**.
Li He; Liu Jun-Ping
Molecular Signaling Laboratory, Baker Medical Research Institute, Prahran, Victoria, Australia.
Biogerontology (Netherlands) 2002, 3 (1-2) p107-16, ISSN 1389-5729
Journal Code: 100930043
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process

Cell aging involves damages and losses of genetic materials including the gradual shortening of telomeres. Telomeres, the ends of chromosomes, have a variety of functions, and the most notable ones include those involved in retaining genome integrity and stability and in regulating **cell** lifespan. Early loss or damage of telomeres causes premature aging, whereas excessive gain of telomeres confers **immortality** upon some cancer **cells** . However, the opposing changes in telomere structures and their associated **cellular** effects on aging and **immortalization** are forcefully regulated by the enzyme telomerase. Telomerase is a large protein-RNA complex that has telomeric

DNA reverse transcriptase activity. Although a wealthy body of information has been obtained on the involvement of telomerase in tumorigenesis, its structure of the holoenzyme, the mode of its action, its **cellular** function in aging, and the pathways of its regulatory mechanisms have not been entirely understood. Recent research on telomerase has become an increasing investigative effort to uncover the molecular mechanisms of aging and aging-related diseases. This article will briefly **review** now telomerase may impact aging, what potential in vivo significance the regulation of telomerase may have on aging, how signals are transduced from telomerase and telomere to **different cellular** effects, and how telomerase itself is controlled in mammalian **cells**.

6/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13167489 21977345 PMID: 11981346
Prospects for the temporary treatment of acute liver failure.
Stockmann Hein B A C; IJzermans Jan N M
Department of Surgery, Erasmus University Medical Centre, Rotterdam, The Netherlands. hein@stockmann.demon.nl
European journal of gastroenterology & hepatology (England) Feb 2002, 14 (2) p195-203, ISSN 0954-691X Journal Code: 9000874
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
At present, the most successful treatment of acute liver failure is orthotopic liver transplantation, with survival rates ranging from 70% to 85%. However, mortality rates for liver failure remain high because of the shortage of available donor organs. Therefore, there has been renewed interest in temporary treatment methods for patients with acute liver failure to either allow liver regeneration or await liver transplantation. It is thought that the function of the liver can only be replaced with the biological substrate, e.g. liver **cells** or a whole liver specimen, which requires the availability of liver tissue from xenogeneic or human sources. In this **review**, existing temporary liver support techniques are summarized and the potential hazards are described. These include the immunological implications of these techniques, e.g. the host versus graft reaction, which may influence the effectivity of the support system, and in the long run may sensitize the patient to subsequent allogeneic transplantation. The graft versus host reaction is also considered. At present, one of the major concerns is the threat of pig-to-human transmission of activated endogenous retrovirus present in the pig genome. An overview is given of literature concerning the transmission of retrovirus particles in vitro and in vivo. Finally, new solutions for the development of ex vivo systems for temporary treatment of patients with acute liver failure are discussed. These include the use of new **immortalized** human **cell** lines and human fetal hepatocytes, and the possibility of isolating, expanding and genetically manipulating stem **cells** in order to have stable **differentiated** and committed **cells**.

6/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12826072 21610051 PMID: 11744088
Interactions between growth factors and steroids in the control of LHRH-secreting neurons.
Melcangi R C; Cavarretta I; Magnaghi V; Martini L; Galbiati M
Department of Endocrinology and Center of Excellence for Neurodegenerative Disorders, University of Milan, Via Balzaretti 9, 20133, Milan, Italy. melcangi@mailserver.unimi.it

Brain research. Brain research reviews (Netherlands) Nov 2001, 37 (1-3) p223-34, ISSN 0165-0173 Journal Code: 8908638
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

How the gene expression and the release of luteinizing hormone releasing hormone (LHRH) are controlled in LHRH-secreting neurons is a very crucial and still debated topic of the neuroendocrinology. Several observations present in literature have recently indicated that glial **cells** may influence the activity of hypothalamic LHRH-secreting neurons, via the release of growth factors. The present **review** will summarize data obtained in our laboratory indicating that: (a) type 1 astrocytes, a kind of glial **cells**, are able to release in vitro growth factors belonging to the transforming growth factors beta (TGFbeta) family (i.e. TGFbeta1 and TGFbeta2) which influence the gene expression and the release of the decapeptide in **immortalized** LHRH-secreting neurons; (b) glial **cells** are also able to influence the steroid metabolism occurring in these neurons and in some cases this effect is exerted by TGFbeta1; (c) the mRNA levels of TGFbeta1 and of basic fibroblast growth factor (bFGF), another growth factor involved in the control of LHRH-secreting neurons, are modified in the rat hypothalamus during the **different** phases of the estrous cycle; (d) steroid hormones are able to modulate the gene expression of TGFbeta1 and bFGF both in vivo (i.e. in the whole hypothalamus of ovariectomized rats) and in vitro (cultures of type 1 astrocytes). On the basis of these results a possible functional correlation in the control of LHRH-secreting neurons between growth factors and gonadal steroids will be discussed and proposed.

6/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12798322 21427890 PMID: 11545165
Isolation of novel developmental genes from human germ **cell**, oocyte and embryo cDNA by **differential** display.
Monk M; Holding C; Goto T
Molecular Embryology Unit, Institute of Child Health, London, UK. mmonk@ich.ucl.ac.uk
Reproduction, fertility, and development (Australia) 2001, 13 (1) p51-7, ISSN 1031-3613 Journal Code: 8907465
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Due to the difficulties inherent in research on human embryos, almost nothing is known about genes active in human early development. Although the human genome project will provide resources that theoretically provide access to every human gene, those genes specific to human early development may be difficult to define. Also, by definition, genes specific to early development will not be represented in cDNA databases derived from human somatic **cells**. Yet these unknown human developmental genes are likely to be of key importance for several areas of human health, including assisted reproduction and contraception, embryo stem **cell** research and tissue transplantation, ageing and cancer. In order to identify and isolate these human developmental genes, we have prepared amplified cDNA from human primordial germ **cells**, oocytes and embryos, and used **differential** display to compare patterns of gene expression in these embryonic **cells** and in the **cells** of somatic tissues of a 10-week human fetus. This paper **reviews** the highly sensitive procedures used to create amplified cDNA representing expressed genes in a single **cell** and the use of **differential** display to identify developmental genes. Several such genes have been isolated, but their full-length sequences and function are yet to be elucidated. Genes active

in human early development are expected to play key roles in the maintenance of the archetypal stem **cell** state, potential **immortality** and the invasiveness of trophectoderm and primordial germ **cells** . They represent candidate genes regulating these functions for targeting in clinical research in human reproduction, stem **cell differentiation** and cancer.

6/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11346768 21411410 PMID: 11520047
Possible applications of conditionally **immortalized** tissue **cell** lines with **differentiation** functions.
Obinata M
Department of Cell Biology, Institute of Development, Aging and Cancer, Tohoku University, 4-1 Seiryo-machi, Aoba-ku Sendai 980-8575, Japan. mobinata@idac.tohoky.ac.jp
Biochemical and biophysical research communications (United States) Aug 31 2001, 286 (4) p667-72, ISSN 0006-291X Journal Code: 0372516
Document type: Journal Article; Review; Review Literature
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
If all individual **cell** types of the body could be clonally isolated and stocked, similar to cDNA or genomic DNA libraries, they would be invaluable for studying the tissue and **cellular** functions. We developed a new method of establishing conditionally **immortalized cell** lines that retain **differentiated cell** functions similar to the original tissues, using temperature-sensitive (ts) simian virus 40 large tumor antigen gene transgenic animals. In this **review** the properties of such conditionally **immortalized cell** lines and their possible applications are discussed. Copyright 2001 Academic Press.

6/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11331106 21384686 PMID: 11493273
Novel strategies for **immortalization** of human hepatocytes.
Cascio S M
MultiCell Associates, Inc., 55 Access Road, Warwick, RI 02886, U.S.A. Stephanie Cascio@brown.edu
Artificial organs (United States) Jul 2001, 25 (7) p529-38, ISSN 0160-564X Journal Code: 7802778
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Normal somatic **cells** have a finite life span due in part to their inability to maintain telomere length and chromosome stability. **Immortalization** strategies based on recent advances in telomere biology and aging research have led to the creation of genetically stable, nontumorigenic **immortalized cell** lines. Reversible **immortalization**, using the Cre-lox recombination and excision system, has been developed for the expansion of primary **cells** for **cell** based clinical therapies. **Immortalized** human hepatocyte **cell** lines with **differentiated** liver functions would find broad applications in biomedical research, especially for pharmacology and toxicology, artificial liver support, and hepatocyte transplantation. The biological basis of these new **immortalization** methods and their application to human hepatocytes is **reviewed**.

6/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11200612 21228694 PMID: 11329939
A new approach to develop a biohybrid artificial liver using a tightly regulated human hepatocyte **cell** line.
Kobayashi N; Noguchi H; Watanabe T; Matsumura T; Totsugawa T; Fujiwara T; Taguchi T; Urata H; Kishimoto N; Hayashi N; Nakaji S; Westerman K A; Leboulch P; Murakami T; Tanaka N
First Department of Surgery, Okayama University Medical School.
Human cell : official journal of Human Cell Research Society (Japan) Dec 2000, 13 (4) p229-35, ISSN 0914-7470 Journal Code: 8912329
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Currently patients with liver failure have been treated with a various liver support systems including a whole liver perfusion, a non-biological artificial liver, and a biohybrid artificial liver. In a hepatocyte-based bioreactor, porcine hepatocytes or transformed human liver tumor **cells** have been utilized because of the ease of preparation. According to the clinical data reported as of now, satisfactory results have not been obtained from the use of currently available liver support devices. One of the problems is limited availability of primary human liver **cells** for developing live support systems because of the shortage of human liver. To resolve this issue, human hepatocytes were **immortalized** with a retroviral vector SSR#69 which contained the genes of simian virus 40 large T antigen (SV40Tag) and herpes simplex virus-thymidine kinase (HSV-TK). One of the **immortal cell** lines, NKNT-3, showed the gene expression of **differentiated** liver functions, grew steadily in chemically defined serum-free CS-C medium, and doubled in number in about 48 hours. Essentially unlimited availability of NKNT-3 **cells** supports their clinical use for liver support devices. To realize the high density culture of NKNT-3 **cells** in a bioartificial liver device, we have developed **cellulose** microspheres (CMS) which contain **cell** adhesive GRGDS (Gly-Arg-Gly-Asp-Ser) peptides. Within 24 hours after starting a stirring suspension culture, GRGDS-CMS efficiently immobilized NKNT-3 **cells** . An electron microscopic examination demonstrated that NKNT-3 **cells** attached on GRGDS-CMS had well-developed mitochondria, rough reticulums, and villous extensions. In this article, we **review** the history of extracorporeal liver support systems and describe an attractive strategy for developing a novel extracorporeal liver assist device using NKNT-3 **cells** and GRGDS-coated **cellulose** microspheres.

6/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11069862 21078300 PMID: 11210944
The hamster polyomavirus--a brief **review** of recent knowledge.
Scherneck S; Ulrich R; Feunteun J
Max Delbruck Center for Molecular Medicine, Berlin, Germany. sschern@mdc-berlin.de
Virus genes (United States) Jan 2001, 22 (1) p93-101, ISSN 0920-8569 Journal Code: 8803967
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The hamster polyomavirus (HaPV) was first described in 1967 as a virus associated with skin epithelioma of the Syrian hamster. The tumors appear spontaneously in a hamster colony bred in Berlin-Buch (HaB). Virus

particles isolated from skin epitheliomas cause lymphoma and leukemia when injected into newborn hamsters from a distinct colony bred in Potsdam, Germany (HaP). The viral genome has been totally sequenced and the overall genetic organization establishes HaPV as a member of the polyomaviruses. HaPV is a second example of an middle T (MT) antigen encoding polyomavirus and nucleotide sequence homologies designates the mouse polyomavirus (Py) as the closest relative. Lymphomas induced by HaPV in HaP hamsters do not contain virus particles but instead accumulate **different** amounts of nonrandomly deleted free and/or integrated viral genomes. Transgenic mice produced by microinjection of HaPV DNA into the pronucleus of fertilized eggs of Gat: NMRI mice developed both, epitheliomas and lymphomas. Both tumor types contain extrachromosomal DNA. HaPV DNA was found to replicate in hamster lymphoid and fibroblast **cell** lines. Fully reproductive cycles could be detected only in GD36 lymphoblastic leukemia **cells**. HaPV carries the full transforming properties of a polyomavirus in vitro. **Immortalization** of primary rat **cells** is essentially carried out by the HaPV large T (LT) antigen and coexpression of HaPV MT and HaPV small T (ST) antigen is required for full transformation of rat fibroblasts. The preferential binding of HaPV MT to c-Fyn, a Src family kinase, has been proposed as a mechanism leading to lymphoid malignancies. Heterologous expression of HaPV-VP1 allowed the formation of virus like particles (VLPs) resembling HaPV particles. The high flexibility of HaPV-VP1 for insertion of foreign peptides offers a broad range of potential applications, especially in vaccine development.

6/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11065028 21076476 PMID: 11212857
Spontaneous neoplastic regression: the significance of apoptosis.
Kaiser H E; Bodey B; Siegel S E; Groger A M; Bodey B
Department of Pathology, School of Medicine, University of Maryland, Baltimore, MD, USA.
In vivo (Athens, Greece) (Greece) Nov-Dec 2000, 14 (6) p773-88, ISSN 0258-851X Journal Code: 8806809
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In mammalian **cells** , neoplastic transformation has a direct relationship with the expression of oncogenes, the production of certain growth factors and with the mutation, loss or simple inactivation of the function of tumor suppressor genes. Genes for suppression of the development of the malignant immunophenotype, as well as inhibitory growth factors have regulatory functions within the normal processes of **cell** division and **differentiation** . Telomerase (a ribonucleoprotein polymerase) activation is frequently observed in various types of neoplastic **cell** transformation. Telomerase activation is regarded as essential for **cell immortalization** and its inhibition may result in spontaneous regression (SR) of neoplasms. SR of neoplasms occurs when the malignant tumor mass partially or completely disappears without any treatment or as a result of a therapy considered inadequate to influence systemic neoplastic disease. This definition makes it clear that the term SR applies to neoplasms in which the malignant disease is not necessarily cured, and to cases where the regression may not be complete or permanent. A number of possible mechanisms of SR are **reviewed**, with the understanding that no single mechanism can completely account for this phenomenon. The application of the newest immunological, molecular biological and genetic insights for more individualized anticancer immunotherapy (biotherapy) is also discussed. In conclusion, of all the possible mechanisms of SR of neoplasms, programmed **cell** death (PCD) or apoptosis is involved in each. The immunological mechanism is probably the main effector mechanism of SR in human neoplasms with its trigger being

apoptosis. The treatments of the tumor, such as with various anti-neoplastic drugs or radiation or immunotherapy, all include the basic mechanism of programmed **cell** death or apoptosis. Without apoptosis, there is practically no tumor regression, none of any kind.

6/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11036498 20584080 PMID: 11150414
Which hepatocyte will it be? Hepatocyte choice for bioartificial liver support systems.
Tsiaoussis J; Newsome P N; Nelson L J; Hayes P C; Plevris J N
Department of Internal Medicine, Liver Unit, Royal Infirmary of Edinburgh, Edinburgh, Scotland.
Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society (UNITED STATES) Jan 2001, 7 (1) p2-10, ISSN 1527-6465 Journal Code: 100909185
Document type: Journal Article; Review; Review Literature
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Liver failure, notwithstanding advances in medical management, remains a cause of considerable morbidity and mortality in the developed world. Although bioartificial liver (BAL) support systems offer the potential of significant therapeutic benefit for such patients, many issues relating to their use are still to be resolved. In this **review**, these issues are examined in terms of the functions required, the **cells** of choice in such a system, and the most appropriate environment to optimize the function of such **cells**. The major functions identified to date for a BAL are ammonia detoxification and biotransformation of toxic compounds, although this somewhat belies the complexity of the functions required. Two practical choices for **cell** type within such a system are xenogenic hepatocytes and **immortalized** human hepatocyte lines. Both these choices have drawbacks, such as the transmission of zoonoses and malignant infiltration, respectively. Finally, improvements in culture conditions, such as supplemented media, biodegradable scaffolds, and coculture, offer the possibility of prolonging the **differentiated** function of hepatocytes in a BAL.

6/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10778336 20345689 PMID: 10887477
The mammary gland: a unique organ for the study of development and tumorigenesis.
Medina D
Department of Cell Biology, Baylor College of Medicine, Houston, Texas 77030, USA.
Journal of mammary gland biology and neoplasia (UNITED STATES) Jan 1996, 1 (1) p5-19, ISSN 1083-3021 Journal Code: 9601804
Contract/Grant No.: CA11944; CA; NCI
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The microanatomy and development of the mammary gland are unique and a reflection of its function to synthesize and deliver milk to the newborn offspring. The uniqueness of the mammary gland resides in several factors. First, the mammary parenchyma undergoes the vast majority of its growth postpubertally, thus enabling experiments on development to be performed in the juvenile or adult and presenting opportunities for experimental

manipulation of the gland not available with other organs. On the basis of this characteristic, the fat pad transplantation method was developed, which resulted in the elaboration of important concepts in senescence, **immortalization** , and preneoplasia. Second, the accessibility of the gland and the ductal organization allows delivery and localization of specific molecules to mammary parenchyma **cells**, the **cells** which are the site of origin of neoplastic development. Third, the organ is the target of viral, chemical, and physical carcinogens, allowing development of unique and complex models for neoplastic development. Finally, the complexity of hormone and growth factor regulation of mammary gland function allows a sophisticated approach to the study of hormone action. The purpose of this **review** is to illustrate some unique properties of the gland which provide the basis for specialized approaches to developmental, neoplastic, and functional problems.

6/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10693266 20227964 PMID: 10762621
Transgenic animal models of human papillomavirus-dependent disease (**Review**) .
Eckert R L; Crish J F; Balasubramanian S; Rorke E A
Department of Physiology/Biophysics, Case Western Reserve University School of Medicine, Cleveland, OH 44106-4970, USA.
International journal of oncology (GREECE) May 2000, 16 (5) p853-70, ISSN 1019-6439 Journal Code: 9306042
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Human papillomaviruses (HPVs) are DNA tumor viruses that induce hyperproliferative lesions in cutaneous and mucosal epithelia. A wide variety of studies implicate the viral E6 and E7 oncoproteins as **cell immortalizing** agents, and show that these proteins work, respectively, by interfering with the function of the p53 and pRb tumor suppressor genes. Most of these studies have been performed using **cell** culture models. However, recently, a variety of in vivo mouse model systems have been developed for the study of HPV-dependent disease. These models use tissue-specific promoters to deliver HPV oncoprotein expression to specific body sites. Using this strategy, mouse models have been designed for the study of cancer progression in epithelia, and additional models have been designed to use E6 and E7, respectively, to probe the role of p53 and pRb on tissue **differentiation** and function. In the present report, we summarize the literature describing these systems, and highlight some of the important findings derived from these studies.

6/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10679504 20216798 PMID: 10751657
Temporal expression of neuronal connexins during hippocampal ontogeny.
Rozental R; Srinivas M; Gokhan S; Urban M; Dermietzel R; Kessler J A; Spray D C; Mehler M F
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Brain research. Brain research reviews (NETHERLANDS) Apr 2000, 32 (1) p57-71, ISSN 0165-0173 Journal Code: 8908638
Document type: Journal Article; Review; Review Literature
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Communication through gap junction channels provides a major signaling mechanism during early brain histogenesis, a developmental time during which neural progenitor **cells** are inexcitable and do not express ligand-gated channel responses to the major CNS neurotransmitters. Expression of **different** gap junction types during neurogenesis may therefore define intercellular pathways for transmission of developmentally relevant molecules. To better understand the molecular mechanism(s) by which growth and **differentiation** of neurons are modulated by gap junction channels, we have been examining the developmental effects of a specific set of cytokines on **differentiation** and gap junction expression in a conditionally **immortalized** mouse embryonic hippocampal neuronal progenitor **cell** line (MK31). When multipotent MK31 **cells** are in an uncommitted state, they uniformly express the neuroepithelial intermediate filament class VI marker, nestin, are strongly coupled by gap junctions composed of connexin43 (Cx43) and express connexin45 (Cx45) at the mRNA level. As these **cells** undergo neuronal lineage commitment and exit from **cell** cycle, they begin to express the early neurofilament marker, NF66, and coupling strength and expression of Cx43 begin to decline with concurrent expression of other connexin proteins, including Cx26, Cx33, Cx36, Cx40 and Cx45. Terminal neuronal **differentiation** is heralded by the expression of more advanced neurofilament proteins, increased morphologic maturation, the elaboration of inward currents and action potentials that possess mature physiological properties, and changing profiles of expression of connexin subtypes, including upregulation of Cx36 expression. These important developmental transitions are regulated by a complex network of **cell** cycle checkpoints. To begin to examine the precise roles of gap junction proteins in traversing these developmental checkpoints and in thus regulating neurogenesis, we have focused on individual members of two classes of genes involved in these seminal events: ID (inhibitor of **differentiation**)-1 and GAS (growth arrest-specific gene)5. When MK31 **cells** were maintained in an uncommitted state, levels of ID-1 mRNA were high and GAS5 transcripts were essentially undetectable. Application of cytokines that promote neuronal lineage commitment and **cell** cycle exit resulted in down-regulation of ID-1 and upregulation of GAS5 transcripts, whereas additional cytokine paradigms that promoted terminal neuronal **differentiation** resulted in the delayed down-regulation of GAS5 mRNA. Stable MK31 transfectants were generated for ID-1 and GAS5. In basal conditions, **cellular** proliferation was enhanced in the ID-1 transfectants and inhibited in the GAS5 transfectants when compared with control MK31 **cells**. When cytokine-mediated neurogenesis was examined in these transfected **cell** lines, constitutive expression of ID-1 inhibited and constitutive expression of GAS5 enhanced initial and terminal stages of neuronal **differentiation** , with evidence that terminal neuronal maturation in both transfectant lines was associated with decreased **cellular** viability, possibly due to the presence of conflicting **cell** cycle-associated developmental signals. These experimental reagents will prove to be valuable experimental tools to help define the functional interrelationships between changing profiles of connexin protein expression and **cell** cycle regulation during neuronal ontogeny in the mammalian brain. The present **review** summarizes the current state of research involving the temporal expression of such connexin types in **differentiating** hippocampal neurons and speculates on the possible role of these intercellular channels in the development and plasticity of the nervous system. In addition, we describe the functional properties and expression pattern of the newly discovered neuronal-specific gap junctional protein, Cx36, in the developing mouse fetal hippocampus and in the rat retina and brain.

6/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10624621 20162703 PMID: 10697595

The roles of telomeres and telomerase in **cellular immortalization** and the development of cancer.

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Anticancer research (GREECE) Nov-Dec 1999, 19 (6A) p4823-30, ISSN 0250-7005 Journal Code: 8102988
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Normal human **cells** have a limited lifespan in culture called the Hayflick limit. Recent studies have indicated that telomere shortening is one of the important meters utilized by **cells** to determine the Hayflick limit, and that activation of a mechanism to maintain telomere length is essential for **cells** to become **immortal** . It is generally believed that **cells** must have a means to maintain telomeres in order to progress to malignancy. Most cancers do this by activating an enzyme called telomerase which adds telomeric repeats to the telomere ends. Recently, expression of this enzyme has been shown to extend the lifespan of **cells**. This **review** discusses the research that led to the discovery of telomerase, the characteristics of telomerase complex, and how recent and future advances in the telomerase field may lead to better diagnostic and treatment protocols for many **different** cancer types.

6/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10624618 20162700 PMID: 10697592

Genetic, epigenetic, dysgenetic and non-genetic mechanisms in tumorigenesis. II. Further delineation of the rate limiting step.

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Anticancer research (GREECE) Nov-Dec 1999, 19 (6A) p4781-9, ISSN 0250-7005 Journal Code: 8102988
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

A not yet understood phenomenon in carcinogenesis is presented by the enormous species-specific and age-specific differences in **cellular** susceptibility to malignant transformation. Murine **cells** are 100,000 times fold more susceptible than human **cells**. A previous **review** article suggested the promotion phase as the key for this difference. Presently, a further analysis of literature data indicates that promotion results in the dedifferentiation of **cells**, which, in initiated **cells**, leads to an imbalanced regenerative growth of stem-**cell** -like **cells** . As aging results in the loss of adaptive functions and in a decreased response to growth stimuli, dedifferentiation of old **cells** is supposed to increase the imbalance of the regenerative growth for initiated **cells** and consequently to enhance the chance for **immortalization** of these **cells**. As **immortalization** is accompanied by chromosomal dysgenetics, malignant conversion by the appearance of secondary genetic events during multistage carcinogenesis is not just a matter of random chance for additional mutations, but is determined to some degree by the condition of the initiated target **cell** and to the species to which the target **cell** belongs.

6/3,AB/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10575904 20102591 PMID: 10639053
Herpes virus latency in sensory ganglia--a comparison with endogenous neuronal gene expression.
Quinn J P; Dalziel R G; Nash A A
Veterinary Pathology, University of Edinburgh, UK. j.quinn@ed.ac.uk
Progress in neurobiology (ENGLAND) Feb 2000, 60 (2) p167-79, ISSN 0301-0082 Journal Code: 0370121
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Central to infection by a majority of DNA viruses is the expression of encoded proteins that modify **cell** cycle. Viruses such as SV40 and Adenovirus viruses encode proteins that interact directly, or indirectly, with key **cell** cycle proteins such as CBP300 and the retinoblastoma gene product. However, neurons do not have a **cell** cycle as we generally describe it and this is also reflected in the difficulty in obtaining **immortalised** neuronal cultures. The replication strategies of viruses that infect post-mitotic **cells** such as neurons may be **different** from infection of other somatic **cells**. The life cycle for viral latency or slow infection of neurons appears to involve silencing or restricting expression of the viral genome until such times as dictated by the environment. These signals from the environment usually reflect **cell** stress, otherwise the **cell** appears to tolerate the existence of the virus genome. We will **review** the genomic structure of alphaherpesviruses in neurons and transcriptional control mechanisms that may regulate expression. Where appropriate we will contrast and compare virus and endogenous neuronal gene expression.

6/3,AB/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10484088 20027736 PMID: 10559636
Immortalized kidney **cells** derived from transgenic mice harboring L-type pyruvate kinase and vimentin promoters.
Vandewalle A
Institut National de la Sante et de la Recherche Medicale, Unite 478, Institut Federatif de Recherche 02, Faculte de Medecine Xavier-Bichat, Paris, France. vandewal@bichat.inserm.fr
Experimental nephrology (SWITZERLAND) Sep-Dec 1999, 7 (5-6) p386-93, ISSN 1018-7782 Journal Code: 9302239
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Targeted oncogenesis in transgenic mice, where an oncogene is placed under the control of the regulatory sequences of a **cell**-specific gene, has been used to derive several new types of **differentiated** nonepithelial and epithelial **cell** lines. This **review** summarizes the properties of **cell** lines derived from proximal, distal and collecting duct **cells**. The **cells** were obtained from kidneys of transgenic mice harboring the 5' regulatory sequences of the L-type pyruvate kinase or vimentin genes controlling the expression of either the large T and little t antigens or the temperature-sensitive large T antigen. Copyright 1999 S. Karger AG, Basel

6/3,AB/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10484078 20007234 PMID: 10541221
Immortalized kidney epithelial **cells** as tools for hormonally regulated ion transport studies.

Vandewalle A; Bens M; Duong Van Huyen J P
Institut National de la Sante et de la Recherche Medicale, Unite 478, Institut Federatif de Recherche 02, Faculte de Medecine Xavier Bichat, Paris, France. vandewal@bichat.inserm.fr
Current opinion in nephrology and hypertension (ENGLAND) Sep 1999, 8 (5) p581-7, ISSN 1062-4821 Journal Code: 9303753
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The development of transgenic mice carrying the simian virus-40 large T antigen gene or the temperature-sensitive simian virus-40 large T antigen gene, either alone or placed under the control of the 5'-regulatory regions of tissue-specific or ubiquitous genes, has permitted the production of **differentiated**, polarized kidney epithelial **cells**. This **review** covers the **immortalized cell** lines issued from the various parts of the renal tubule and, in particular, the recently established collecting duct **cell** lines that have been used as ex-vivo **cell** models to analyze the regulation of ion transport processes by hormones.

6/3,AB/24 (Item 24 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10459910 99444590 PMID: 10515001
Prospects for the clinical application of neural transplantation with the use of conditionally **immortalized** neuroepithelial stem **cells**.
Gray J A; Hodges H; Sinden J
Department of Psychology, Institute of Psychiatry, London, UK.
Philosophical transactions of the Royal Society of London. Series B: Biological sciences (ENGLAND) Aug 29 1999, 354 (1388) p1407-21, ISSN 0962-8436 Journal Code: 7503623
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Although neural transplantation has made a relatively successful transition from the animal laboratory to human neurosurgery for the treatment of Parkinson's disease, the use of human embryonic brain tissue as the source of transplants raises difficult ethical and practical problems. These are likely to impede the widespread use of this otherwise promising therapy across the range of types of brain damage to which the results of animal experiments suggest its potential applicability. Various alternative approaches are **reviewed** briefly, aimed at developing sources of tissue for transplantation that can be maintained in vitro until needed, so obviating the requirement for fresh embryonic tissue at each occasion of surgery. Particularly promising are conditionally **immortalized** neuroepithelial stem **cell** lines in which the **immortalizing** gene is downregulated upon transplantation into a host brain. We describe experiments from our laboratory with the use of **cells** of this kind, the multipotent MHP clonal **cell** lines, derived from the developing hippocampus of a transgenic mouse harbouring a temperature-sensitive oncogene. Implanted into the hippocampus of rats and marmosets with damage to the CA1 **cell** field, the MHP36 line gave rise to healthy surviving grafts and to essentially complete recovery of cognitive function. Postmortem study of the implanted rat brains indicated that MHP36 **cells** migrate to the region of damage, adopt both neuronal (pyramidal) and glial phenotypes in vivo, and reconstitute the normal laminated appearance of the CA1 **cell** field. We have previously shown that, when primary **differentiated** foetal tissue is used as the source of grafts in rats with CA1 damage, there is a stringent requirement for replacement with homotypic CA1 **cells**. We interpret our results as showing that the MHP36 **cell** line responds to putative signals

associated with damage to the hippocampus and takes up a phenotype appropriate for the repair of this damage; they therefore open the way to the development of a novel strategy with widespread applicability to the treatment of the diseased or damaged human brain.

6/3,AB/25 (Item 25 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10356335 99343436 PMID: 10416993
Genetic regulatory elements introduced into neural stem and progenitor **cell** populations.
Foster G A; Stringer B M
Cardiff School of Biosciences, University of Wales, UK. FosterGA@Cardiff.ac.uk
Brain pathology (Zurich, Switzerland) (SWITZERLAND) Jul 1999, 9 (3) p547-67, ISSN 1015-6305 Journal Code: 9216781
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The genetic manipulation of neural **cells** has advantage in both basic biology and medicine. Its utility has provided a clearer understanding of how the survival, connectivity, and chemical phenotype of neurones is regulated during, and after, embryogenesis. Much of this achievement has come from the recent generation by genetic means of reproducible and representative supplies of precursor **cells** which can then be analyzed in a variety of paradigms. Furthermore, advances made in the clinical use of transplantation for neurodegenerative disease have created a demand for an abundant, efficacious and safe supply of neural **cells** for grafting. This **review** describes how genetic methods, in juxtaposition to epigenetic means, have been used advantageously to achieve this goal. In particular, we detail how gene transfer techniques have been developed to enable **cell immortalization** , manipulation of **cell differentiation** and commitment, and the controlled selection of **cells** for purification or safety purposes. In addition, it is now also possible to genetically modify antigen presentation on **cell** surfaces. Finally, there is detailed the transfer of therapeutic products to discrete parts of the central nervous system (CNS), using neural **cells** as elegant and sophisticated delivery vehicles. In conclusion, once the epigenetic and genetic controls over neural **cell** production, **differentiation** and death have been more fully determined, providing a mixture of hard-wired elements and more flexibly expressed characteristics becomes feasible. Optimization of the contributions and interactions of these two controlling systems should lead to improved **cell** supplies for neurotransplantation.

6/3,AB/26 (Item 26 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10327053 99309975 PMID: 10382602
Review: Theileria schizonts induce fundamental alterations in their host **cells**.
Ahmed J S; Schnittger L; Mehlhorn H
Forschungszentrum Borstel, Germany. jahmed@fz-borstel.de
Parasitology research (GERMANY) Jul 1999, 85 (7) p527-38, ISSN 0932-0113 Journal Code: 8703571
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The sporozoites of Theileria annulata and T. parva invade bovine leukocytes, where they **differentiate** into schizonts. The latter can

immortalize and induce fundamental changes in their host **cells**. T. annulata infects mainly major histocompatibility complex class II **cells** , whereas T. parva preferentially transforms T-lymphocytes, which proliferate continuously without the need for exogenously added growth factors. Most of the **cell** lines appear to be independent of a growth factor but may express several cytokines that influence the outcome of the disease. The mechanisms underlying this transformation are not well understood. The infected **cells** show increased activity of casein kinase II and Jun NH2-terminal kinase (JNK), whereas extracellular signal-related kinase 1 and 2 and P38 are not activated. In addition, several transcriptional factors such as NFkB and AP-1 are activated. It has been postulated that parasite proteins either expressed on the surface of the schizonts or secreted into the host **cell** cytoplasm may interfere with the signal-transduction pathway of the host **cells**. A possible candidate may the casein kinase II homologue that was identified in schizonts of both T. annulata and T. parva.

6/3,AB/27 (Item 27 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10305042 99305040 PMID: 10378695
The v-myc oncogene.
Lee C M; Reddy E P
Fels Institute for Cancer Research and Molecular Biology, School of Medicine, Temple University, Philadelphia, Pennsylvania 19140, USA.
Oncogene (ENGLAND) May 13 1999, 18 (19) p2997-3003, ISSN 0950-9232 Journal Code: 8711562
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
v-myc is the viral homolog of c-myc transduced by several acute transforming retroviruses, many of which encode this gene as a Gag-Myc fusion protein. The v-myc oncogene can transform several lineages of mammalian and avian **cells** either alone or in cooperation with other oncogenes. While the Gag portion of the Gag-Myc fusion protein and the nuclear localization signal each appear to be dispensable for transformation, the N- and C-termini of the Myc sequence have been found to be essential for transformation. All v-myc genes contain point mutations which seem to confer a greater potency to v-myc in the process of transformation, proliferation, and apoptosis. In v-myc-transformed myelomonocytic **cells**, secondary events occur, such as the expression of colony stimulating factor-1 (CSF-1) which play a critical role in **immortalization** and subsequent tumor progression. Inhibition of the autocrine loop of CSF-1 was found to induce apoptosis in the **immortalized cells** . While overexpression of v-Myc blocks terminal **differentiation** of hematopoietic **cells**, this is not sufficient to block the **differentiation** of certain neural and skeletal muscle **cells**. Recent developments on the effects of v-myc on **cell** growth, transformation, **differentiation** and apoptosis are discussed in this **review**.

6/3,AB/28 (Item 28 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10305035 99305033 PMID: 10378688
The Myc oncoprotein: a critical evaluation of transactivation and target gene regulation.
Cole M D; McMahon S B
Department of Molecular Biology, Princeton University, New Jersey 08544-1014, USA.
Oncogene (ENGLAND) May 13 1999, 18 (19) p2916-24, ISSN 0950-9232

Journal Code: 8711562
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Mutations which disrupt the regulation or expression level of the c-myc gene are among the most common found in human and animal cancers (**reviewed** in ref. Cole, 1986; Henriksson and Luscher, 1996; Marcu et al., 1992). Ectopic expression studies define numerous biological activities of the c-myc gene, including transformation, **immortalization**, blockage of **cell differentiation** and induction of apoptosis (Askew et al., 1991; Cole, 1986; Evan and Littlewood, 1993; Freytag et al., 1990; Henriksson and Luscher, 1996; Marcu et al., 1992). Furthermore, c-myc is required for efficient progression through the **cell** cycle (Goruppi et al., 1994; Prochownik et al., 1988; Yokoyama and Imamoto, 1987), although recent studies indicate that it is not absolutely essential (Mateyak et al., 1997). This fascinating array of biological activities makes the c-myc gene one of the most intriguing oncogenes and presents the challenging question of how a single gene can manifest so many **different** effects. The c-Myc protein exhibits sequence-specific DNA binding when dimerized with its partner Max, and DNA binding is mediated through the basic region, which recognizes the core sequence CACGTG (Berberich et al., 1992; Blackwell et al., 1993; Blackwood and Eisenman, 1991; Prendergast and Ziff, 1991; Prendergast et al., 1991), but exhibits somewhat higher affinity for the more extended sequence ACCACGTGGT (Berberich et al., 1992; Blackwell et al., 1993; Halazonetis and Kandil, 1991). There are three closely related Myc family proteins (c-Myc, N-Myc and L-Myc), each with documented oncogenic potential (Birrer et al., 1988; Schwab et al., 1985; Yancopoulos et al., 1985) and similar DNA binding properties (Mukherjee et al., 1992). For simplicity, we will use the term Myc to refer to all three proteins, but delineate any distinct activities where they apply. The goal of this **review** is to discuss Myc as a transcriptional activator and critically evaluate the evidence for the transactivation of specific target genes as direct downstream effectors. Since excellent comprehensive **reviews** on Myc have been published recently (Facchini and Penn, 1998; Henriksson and Luscher, 1996), we will focus on the latest observations that offer mechanistic insight into transactivation and oncogenic transformation.

6/3,AB/29 (Item 29 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10005593 99005503 PMID: 9787089

Efficacy of grafted **immortalized** dopamine neurons in an animal model of parkinsonism: a **review**.

Prasad K N; Clarkson E D; La Rosa F G; Edwards-Prasad J; Freed C R
Center for Vitamins and Cancer Research, University of Colorado Health Sciences Center, Denver, Colorado 80262, USA.

Molecular genetics and metabolism (UNITED STATES) Sep 1998, 65 (1) p1-9, ISSN 1096-7192 Journal Code: 9805456
Contract/Grant No.: RO1 NS 18639; NS; NINDS; RO1 NS 29982; NS; NINDS; RO1 NS 35348; NS; NINDS
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Dopamine (DA) deficiency is one of the primary lesions in the pathogenesis of Parkinson disease (PD). Because of long-term toxicity of L-DOPA therapy, the grafting of fetal mesencephalic tissue containing dopamine neurons or homogeneous populations of DA neurons into striatum appears to be rational. Fetal tissue transplants have many problems which include legal (in some countries), ethical, paucity of tissue availability, heterogenicity of **cell** populations, and the presence of

antigen-presenting **cells** that are responsible for rejection of allogeneic grafts. In order to resolve the above problems, we have established **immortalized** DA neurons from fetal rat mesencephalon by inserting the large T-antigen (LTa) gene of the SV40 virus into the **cells** . A clone of DA neurons (1RB3AN27) was isolated, characterized, and tested in 6-hydroxydopamine (6-OHDA)-lesioned rats (a model of PD). These **cells** divided with a doubling time of about 26 h, expressed the LTa gene, and contained the tyrosine hydroxylase and dopamine transporter proteins and their respective mRNAs, which became elevated upon **differentiation**. These **cells** were nontumorigenic and nonimmunogenic and improved the symptoms of neurological deficits (methamphetamine-induced rotation) in 6-OHDA-lesioned rats. The **differentiated** DA neurons were more effective than undifferentiated ones. These studies suggest that **immortalized** DA neurons generated in vitro by LTa gene insertion may be used in transplant therapy without fear of tumor formation or rejection. Copyright 1998 Academic Press.

6/3,AB/30 (Item 30 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09946635 98396766 PMID: 9728594
B-**cell** development and maturation.
Rudin C M; Thompson C B
Gwen Knapp Center for Lupus and Immunology Research, the Department of Medicine, Howard Hughes Medical Institute, University of Chicago, IL 60637, USA.
Seminars in oncology (UNITED STATES) Aug 1998, 25 (4) p435-46, ISSN 0093-7754 Journal Code: 0420432
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Approximately 85% of all non-Hodgkin's lymphomas arise from **cells** of the B lineage. Sequential stages of B-**cell** development have been defined by molecular markers, and these markers can be used to reclassify lymphoid malignancies as representing maturational arrest and **immortalization** at specific points in B-**cell** ontogeny. Several of the factors controlling the ordered rearrangement and expression of the immunoglobulin (Ig) genes have been identified. Signals generated by intermediates in Ig gene rearrangement, as well as by the complete Ig molecule, have been found to be critical in guiding early B-**cell** development. The processes of peripheral B-**cell** activation, antigenic affinity maturation, and terminal B-**cell** **differentiation** are also highly regulated. The molecular mechanisms responsible for both promoting and attenuating B-**cell** (humoral) immune responses have been increasingly well defined. This **review** summarizes some aspects of the current understanding of normal B-**cell** development, maturation, activation, and death, focusing on the factors implicated in regulating progression through these stages.

6/3,AB/31 (Item 31 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09926758 98348067 PMID: 9684925
In vitro effects of retinoids on the proliferation and **differentiation** features of Epstein-Barr virus-**immortalized** B lymphocytes.
Dolcetti R; Zancai P; Cariati R; Boiocchi M
Division of Experimental Oncology 1, Centro di Riferimento Oncologico, Aviano (PN) Italy.
Leukemia & lymphoma (SWITZERLAND) Apr 1998, 29 (3-4) p269-81, ISSN 1042-8194 Journal Code: 9007422

Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Retinoids have been shown to be effective in the chemoprevention and treatment of certain human malignancies. In this **review**, we will summarize our recent results concerning the effects of retinoids on the proliferation and **differentiation** of Epstein-Barr virus (EBV)-**immortalized** lymphoblastoid B-**cell** lines (LCLs), an in vitro model of EBV-related lymphoproliferative disorders arising in immunosuppressed hosts. Retinoids proved to be powerful inhibitors of the proliferation of EBV-infected LCLs in vitro, with 13-cis-retinoic acid (RA), all-trans-RA, and 9-cis-RA being the most effective compounds. Of note, retinoid-induced growth arrest in vitro appears irreversible at drug concentrations (10(-6) mol/L) which may be reached in man after oral systemic therapy. The antiproliferative activity exerted by retinoids on LCLs is a generalized phenomenon usually associated with a progressive accumulation in G0/G1 phases of treated **cells** . The strong upregulation of p27Kip1 invariably observed in **cells** exposed to retinoids may contribute to the decreased number of cycling **cells**, probably by inhibiting the transition from the G1 to S phase. Moreover, we obtained evidence indicating that the antiproliferative effects of retinoids are not dependent on the induction of terminal **differentiation** of EBV-**immortalized** B lymphocytes. In fact, the modifications induced by retinoids relative to LCL morphology, phenotype (downregulation of CD19, HLA-DR, and s-Ig, and upregulation of CD38 and c-Ig), and IgM production were highly variable among the lines tested and often only slightly relevant. Finally, the antiproliferative activity exerted by retinoids on LCLs is not mediated by a direct modulation of viral latent antigens, since EBNA-2 and LMP- downregulation was a late event detected only in some **cell** lines. These results indicate that retinoids may be useful in the medical treatment of EBV-related lymphoproliferative disorders of immunosuppressed patients, particularly in the earlier phases of these diseases.

6/3,AB/32 (Item 32 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09914805 98352975 PMID: 9690665

Cell kinetics of prostate exocrine and neuroendocrine epithelium and their **differential** interrelationship: new perspectives.

Xue Y; Smedts F; Verhofstad A; Debruyne F; de la Rosette J; Schalken J
Department of Urology, University Hospital Nijmegen, The Netherlands.

Prostate. Supplement (UNITED STATES) 1998, 8 p62-73, ISSN 1050-5881
Journal Code: 9003050
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The prostate gland consists of a complex ductal system lined with exocrine basal and luminal **cells**, and neuroendocrine epithelial **cells**. This paper **reviews** the histologic and molecular **cell** biologic characteristics of these **cells**, in normal adult tissue, during prostate morphogenesis, and in the development of benign and malignant neoplastic conditions. Expression of **differentiation** markers, as well as proliferation and apoptosis markers, growth factors and associated receptors, and abnormalities in genes and chromosomes are **reviewed**. Accumulating data indicate that (1) pluripotent **immortal** stem **cells** are located in the basal **cell** compartment of the prostate; (2) there is a subpopulation of epithelial **cells** in the prostate gland (intermediate **cells**) that have both structural and functional characteristics common to basal and luminal **cells**, which may be identified in various conditions; and prostate NE

cells may have the same common origin as other exocrine **cells**, and share the same **differentiation** pathway. A stem **cell** model is proposed in which both exocrine and endocrine **cells** are derived from a subpopulation of basal **cells** (stem **cell**) that give rise to luminal **cells** through intermediate **cells** (pluripotent amplifying **cells**). These **cells** are also probably highly implicated in the early development of prostate benign and malignant neoplasia.

6/3,AB/33 (Item 33 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09856471 98301281 PMID: 9639410
Review of alterations of the cyclin-dependent kinase inhibitor INK4 family genes p15, p16, p18 and p19 in human leukemia-lymphoma **cells**.
Drexler H G
DSMZ-German Collection of Microorganisms and Cell Cultures, Department of Human and Animal Cell Cultures, Braunschweig, Germany.
Leukemia : official journal of the Leukemia Society of America, Leukemia Research Fund, U.K (ENGLAND) Jun 1998, 12 (6) p845-59, ISSN 0887-6924 Journal Code: 8704895
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The cyclin-dependent kinase inhibitors known as p15, p16, p18 and p19 have been suggested as candidates for tumor suppressor genes. The main genetic alterations are deletions (bi- or monoallelic) or 5' CpG island methylation of p15 and p16; very few cases or **cell** lines had p18 or p19 deletions or hypermethylation. Hypermethylation and homozygous deletions of tumor suppressor genes establish a new paradigm of inactivation by lack of expression, in contrast to the previously identified tumor suppressors which are predominantly inactivated by point mutations followed by loss of the wild-type allele. Here, the literature data on alterations of this gene family in more than 4700 primary cases of leukemia or lymphoma and some 320 continuous leukemia-lymphoma **cell** lines are summarized. Among hematopoietic malignancies, the highest frequencies of p15del and p16del were seen in acute lymphoblastic leukemia (ALL) (>30%) with striking rates in T-ALL (>50%), but also high rates in B **cell** precursor (BCP)-ALL (>20%); the rates of deletions in chronic lymphoid leukemia (CLL), multiple myeloma, acute and chronic myeloid leukemia (AML and CML), and myelodysplastic syndromes (MDS) were rather low, only some B **cell** and T **cell** lymphomas showed increased frequencies. Results are quite **different** with regard to the second mode of inactivation, hypermethylation of the promoter region. Here, p15 is most often inactivated, at particularly high frequencies in the disorders lacking any p15/p16 deletions: 40-80% p15met in AML, MDS and multiple myeloma. Also p15met rates in BCP- and T-ALL cases were high (c. 40%). There is controversy concerning the prognostic impact of p15 and p16 aberrations with some studies describing a significant correlation between inactivation of these genes and poor prognosis, while most others did not detect any prognostic relevance, at least in pediatric ALL; there may be a worse prognosis for adults with B or T **cell** lymphomas. Despite the small number of cases studied, paired sequential analyses suggested that disease progression is associated with loss of p15/p16 activity in a certain percentage of adult patients. p15del/p16del and p15met/p16met were also detected in the large panel of leukemia-lymphoma **cell** lines studied. In general, the results in **cell** lines reproduce the data seen in primary **cells** with the important difference that the rates of p15/p16 inactivation are clearly higher in the cultured **cells** compared with the freshly explanted **cells** . Retrovirus- or electroporation-mediated ectopic gene transfer of p16 wild-type into p16-deficient **cell** lines led to growth inhibition, arrest in G1

(without apoptosis) and occasionally to **differentiation**, suggesting that the malignant phenotype of p16-/- **cell** lines can, at least partially, be reversed by restoring p16 gene expression. A striking inverse correlation between the absence of p16 (due to deletion) and presence of wild-type retinoblastoma gene was observed in **cell** lines confirming a common growth suppressor pathway; no comparable relationship of p16 inactivation with p53 was detected. Paired analysis of **cell** lines and corresponding primary **cell** material showed that in all instances tested both populations carried the same gene configuration of p15 and p16. Thus, p15del or p16del did not occur during establishment of the **cell** lines or during prolonged culture. It is likely that p15 or p16 deletions already acquired in vivo provide a dramatic growth advantage for the **immortalization** process in vitro, thus increasing the success rate for **cell** line establishment which is commonly extremely difficult. In conclusion, the present **review** suggests an involvement of the p15 and p16 tumor suppressor genes in leukemo- and lymphomagenesis. Future studies will determine their exact role in the development and progression of hematopoietic neoplasms. These genes may represent interesting targets for new therapeutic strategies.

6/3,AB/34 (Item 34 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09821769 98263859 PMID: 9601553
In vitro systems and cultured **cells** as specimens for X-ray microanalysis.
Roomans G M; Hongpaisan J; Jin Z; Mork A C; Zhang A
Department of Human Anatomy, University of Uppsala, Sweden. godfried.roomans@anatomi.uu.se
Scanning microscopy. Supplement (UNITED STATES) 1996, 10 p359-70; discussion 370-3, ISSN 0892-953X Journal Code: 8710881
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In vitro systems and cultured **cells** are recognized as useful systems in many areas of biomedical research, including X-ray microanalysis. To be reliable, in an vitro system should have an elemental composition close to that of the tissue in situ, react in the same way to stimuli, and retain the in situ regulation of ion transport. In the present paper, four of the most commonly used in vitro systems will be **reviewed** : incubated tissue slices (liver and pancreas), isolated glands (submandibular gland acini, sweat glands), primary **cell** cultures (sweat glands, endometrium), and **cell** lines (the colon cancer **cell** line T84, **immortalized** sweat gland **cells**).
Incubation of tissue slices of liver in Krebs-Ringers buffer caused a significant increase in Na and Cl and a decrease in K. Initially, these changes were also observed in the pancreas, but here the values gradually returned to normal. Isolated submandibular gland acini, and isolated sweat gland ducts and coils react in a similar way to stimulation as their in situ counterparts. In primary cultures of coil **cells**, however, part of the **cell** population acquires **different** ion transport characteristics. Technically simplest is the use of **cell** lines originating from cancer **cells** (e.g., the T84 **cell** line) and **immortalized** **cell** lines. X-ray microanalysis not only confirms data on ion transport obtained with other techniques, but adds the possibility to investigate the presence of subpopulations within a culture.

6/3,AB/35 (Item 35 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09806023 98236345 PMID: 9575433

The spontaneous regression of neoplasms in mammals: possible mechanisms and their application in immunotherapy.
Bodey B; Bodey B; Siegel S E; Kaiser H E
Department of Pathology, School of Medicine, University of Southern California, Los Angeles, USA.
In vivo (Athens, Greece) (GREECE) Jan-Feb 1998, 12 (1) p107-22, ISSN 0258-851X Journal Code: 8806809
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In mammalian **cells** , neoplastic transformation is directly associated with the expression of oncogenes, with the mutation, loss or simple inactivation of the function of tumor suppressor genes, and the production of certain growth factors. Genes for suppression of the development of the malignant immunophenotype, as well as inhibitory growth factors have regulatory functions within the normal processes of **cell** division and **differentiation** . Telomerase (a ribonucleoprotein polymerase) activation is frequently observed in various cancers. Telomerase activation is regarded as essential for **cell immortalization** and its inhibition may result in the spontaneous regression (SR) of neoplasms. SR of neoplasms occurs when the malignant tumor mass partially or completely disappears without any treatment or as a result of a therapy considered inadequate to influence systemic neoplastic disease. This definition makes it clear that the term SR applies to neoplasms in which the malignant disease is not necessarily cured, and to cases where the regression may be neither complete nor permanent. A number of possible mechanisms of SR are **reviewed**, with the understanding that no single mechanism can completely account for this phenomenon. The application of the newest immunological, molecular biological and genetic insights for more individualized anticancer immunotherapy (biotherapy) is also discussed.

6/3,AB/36 (Item 36 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09652067 98087811 PMID: 9426431
Telomerase activity in benign and malignant thyroid diseases.
Yashima K; Vuitch F; Gazdar A F; Fahey T J
Hamon Center for Therapeutic Oncology Research, University of Texas Southwestern Medical Center, Dallas, USA.
Surgery (UNITED STATES) Dec 1997, 122 (6) p1141-5; discussion 1145-6 , ISSN 0039-6060 Journal Code: 0417347
Contract/Grant No.: N01-CN-45580-01; CN; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
BACKGROUND: Telomerase, an enzyme associated with **cellular immortality**, is expressed by most malignant **cells** and is inactive in most normal somatic **cells** , with the excitation of proliferative stem **cells**, male germ **cells** , and activated lymphocytes. The measurement of telomerase activity in clinically obtained tissue samples may provide useful information as both a diagnostic and prognostic marker. In this study, we sought to determine whether telomerase activity might prove helpful in the assessment of benign and malignant thyroid tumors. METHODS: A modified, semiquantitative polymerase chain reaction-based telomeric repeat amplification protocol assay was used for detection of telomerase activity in 59 samples obtained at thyroidectomy, including 15 thyroid cancers, 22 benign thyroid diseases, and 22 adjacent normal thyroid tissues. RESULTS: Four of 13 **differentiated** thyroid carcinomas (30%) and 2 of 2 medullary carcinomas (100%) expressed telomerase activity. Unexpectedly, we also detected activity in 3 of 22

(14%) adjacent normal thyroid tissues and 6 of 22 (28%) benign thyroid diseases. Pathologic **review** of the telomerase-positive benign specimens revealed that many contained extensive lymphoid infiltrates with germinal centers (six of nine, 67%), as did two of four telomerase-positive papillary carcinomas. CONCLUSIONS: In contradistinction to other epithelial carcinomas, telomerase does not appear to be frequently reactivated in **differentiated** thyroid carcinomas.

6/3,AB/37 (Item 37 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09627642 98046407 PMID: 9390819
Production of conditionally **immortalised cell** lines from a transgenic mouse.
Holley M C; Lawlor P W
Department of Physiology, School of Medical Sciences, University of Bristol, UK. m.c.holley@bristol.ac.uk
Audiology & neuro-otology (SWITZERLAND) Jan-Apr 1997, 2 (1-2) p25-35 , ISSN 1420-3030 Journal Code: 9606930
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
This **review** describes the H2kbtsA58 transgenic mouse (Immortomouse) and its application to the production of conditionally **immortalised cell** lines from sensory epithelia within the mammalian inner ear. Established **cell** lines should overcome many of the technical difficulties associated with experimental procedures in auditory and vestibular research. These include the limited amount of tissue available and the relatively complex and laborious dissection. Conditional **immortalisation** should also allow essential studies on the molecular and **cellular** mechanisms that govern both the **differentiation** of sensory **cells** and the development of sensory epithelia.

6/3,AB/38 (Item 38 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09598852 98032238 PMID: 9365534
Telomerase in human development and cancer.
Shay J W
Department of Cell Biology and Neuroscience, University of Texas Southwestern Medical Center at Dallas 75235, USA.
Journal of cellular physiology (UNITED STATES) Nov 1997, 173 (2) p266-70, ISSN 0021-9541 Journal Code: 0050222
Contract/Grant No.: AG07992; AG; NIA
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A potentially rate-limiting step in cancer progression is the conversion of a normal human **cell** into one capable of indefinite proliferation. There are at least two **different cellular** mechanisms that must be overcome before **immortalization** occurs. The first step generally requires inactivation of the pathways involving two tumor-suppressor genes, p53 and pRB, and the second step almost always involves the reactivation of the ribonucleoprotein enzyme telomerase. Telomerase synthesizes hexameric repeats (TTAGGG) onto telomeric ends, thereby compensating for telomeric losses that in its absence occurs at each **cell** division. Telomerase is present in human embryonic tissues, is not detected in most adult tissues, but is upregulated or reactivated in almost 90% of all human cancers. In the present article, I **review** the telomere-telomerase theory of aging and cancer including the roles of telomerase during human

development, in **differentiation** , and in cancer. Research into the regulation of this enzyme may lead to methods to facilitate the accurate diagnosis of cancer and to the development of novel antitelomerase cancer therapeutics.

6/3,AB/39 (Item 39 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09492343 97403237 PMID: 9258606
Oncogene-initiated aberrant signaling engenders the metastatic phenotype: synergistic transcription factor interactions are targets for cancer therapy.
Denhardt D T
Department of Cell, Developmental and Neurobiology, Nelson Biological Laboratories, Rutgers University, Piscataway, NJ 08854, USA.
Critical reviews in oncogenesis (UNITED STATES) 1996, 7 (3-4) p261-91, ISSN 0893-9675 Journal Code: 8914610
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Certain p21GTPases (notably Ras) and some of their guanine nucleotide exchange factors (e.g., Ost, Dbl, Tiam) and downstream mediators (e.g., Raf, Myc) have the potential to promote the development of malignancies because they can enhance the transcription of genes that foster the tumorigenic and metastatic phenotype. Among these are genes that stimulate **cell** proliferation, confer **immortality** , and facilitate the invasion of normal tissues. Oncogenes upstream of Ras-**cell** surface receptors such as ErbB2/Neu, Met, or Trk (and their ligands), and nonreceptor cytoplasmic protein tyrosine kinases such as Src and Abl-not only can act through Ras but also contribute additional signals. This **review** presents a synopsis of our understanding of signaling pathways controlled by the p21GTPases, with a focus on transcription factors regulated by the pathways. Mutations in one or more of the elements in these signaling pathways are invariably found in cancer **cells**. Crosstalk among the pathways may explain how some forms of stress can contribute to the development of a malignancy. Abnormal signaling leads to modified cytoskeletal structures and permanently altered (i.e., self-sustaining or epigenetic) transcription of target genes. A common therne is that genes whose transcription is elevated to the greatest extent by Ras often have in their promoters juxtaposed binding sites for two **different** transcription factors (particularly those in the Fos/Jun, CREB/ATF, NFkB, and Ets families) each of which is activated and such that together they synergize to augment transcription substantially. Some of these transcription factors can also act as oncogenes in certain **cell** types when appropriately modified and expressed. This unifying theme among many **different** cancers suggests that strategies to restore the balance among the signaling pathways or to suppress synergistic interactions between transcription factors may prove broadly useful in reversing the malignant phenotype.

6/3,AB/40 (Item 40 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09392459 97276551 PMID: 9130304
Cognitive deficits induced by global cerebral ischaemia: prospects for transplant therapy.
Hodges H; Nelson A; Virley D; Kershaw T R; Sinden J D
Department of Psychology, Institute of Psychiatry, London, UK.
Pharmacology, biochemistry, and behavior (UNITED STATES) Apr 1997, 56 (4) p763-80, ISSN 0091-3057 Journal Code: 0367050
Document type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Global ischaemia induced by interruption of cerebral blood flow results in damage to vulnerable **cells** , notably in the CA1 and hilar hippocampal fields, and is frequently associated with memory deficits. This **review** examines cognitive deficits that occur in animal models of global ischaemia in rats and monkeys, the extent to which these deficits are associated with CA1 **cell** loss, and the evidence for functional recovery following transplants of foetal CA1 **cells** and grafts of conditionally **immortalised** precursor **cells** . In rats, impairments are seen most consistently in tasks of spatial learning and spatial working memory dependent on use of allocentric environmental cues. In monkeys, ischaemic deficits have been shown to a moderate extent in delayed object recognition tasks, but animals with a selective excitotoxic CA1 lesion show a profound impairment in conditional discrimination tasks, suggesting that these may be a more sensitive measure of ischaemic impairments. Several studies have reported correlational links between the extent of CA1 **cell** loss following two or four vessel occlusion (2 VO, 4 VO) in rats and behavioural impairments, but recent findings indicate that at intermediate levels of damage these relationships are weak and variable, and emerge clearly only when animals with maximal CA1 **cell** loss are included, suggesting that the deficits involve more than damage to the CA1 field. Nevertheless, ischaemic rats and CA1-lesioned marmosets with grafts of foetal CA1 **cells** show substantial improvements; in rats these are not found with grafts from other hippocampal fields. Conditionally **immortalised** **cell** lines and trophic grafts are currently being assessed for their functional potential in animal models, because clinical use of foetal **cells** will not be practicable. Recent findings suggest that an expanded population of neuroepithelial **cells** derived from the conditionally **immortalised** H-2Kb-tsA58 transgenic mouse improve spatial learning as effectively as CA1 foetal grafts in rats subjected to 4 VO, and clonal lines from the same source show similar promise. Lines derived from precursor **cells** have the potential to develop into **different** types of **cell** (neuronal or glial) depending on signals from the host brain. These **cell** lines may therefore have the capacity to repair damaged host circuits more precisely than is possible with foetal grafts, and offer a promising, approach both to functional recovery and to elucidating graft-host interactions.

6/3,AB/41 (Item 41 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09367783 97244095 PMID: 9088906
Expression of endothelin, fibronectin, and mortalin as aging and mortality markers.
Kumazaki T; Wadhwa R; Kaul S C; Mitsui Y
Department of Biochemistry and Biophysics, Hiroshima University, Japan.
Experimental gerontology (ENGLAND) Jan-Apr 1997, 32 (1-2) p95-103, ISSN 0531-5565 Journal Code: 0047061
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Studies on fibronectin, endothelin-1, and mortalin from our laboratory are **reviewed** here. Fibronectin expression has been analyzed as upregulated during in vitro serial passaging of human fetal lung and neonatal foreskin fibroblasts as well as umbilical vein endothelial **cells** . In vivo aging of skin fibroblasts, as well as aortic endothelial **cells** , are also accompanied by upregulation of fibronectin expression. Fibronectin promoter binding proteins from young and old **cell** nuclear extracts were further explored by gel retardation assay. Preliminary analyses have detected age-related

differential binding activities with respect to AP-1, CRES, TFIID, CTF, and AP-2 regions, whereas Sp1 binding proteins remain unaltered. Endothelin-1 expression is also seen as upregulated during in vitro and in vivo aging of endothelial **cells** . This can contribute to the hypertension commonly observed in elderly patients. Mortalin, a novel member of hsp 70 family of proteins, was initially identified by virtue of its association with a **cellular** mortal phenotype. Subsequently, normal **cells** and the ones with an **immortal** phenotype have been found to have **differential** subcellular localization of this protein. Antiproliferative activity of this protein in normal **cells** and the deregulation of expression in transformed **cells** is observed which suggests the association of mortalin in pathways that determine **cellular** divisional phenotype.

6/3,AB/42 (Item 42 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09251415 97164824 PMID: 9012586
Genetic, epigenetic, dysgenetic, and non-genetic mechanisms in tumorigenesis.
Simons J W
Department of Radiation Genetics and Chemical Mutagenesis, MGC., Leiden University, The Netherlands.
Critical reviews in oncogenesis (UNITED STATES) 1995, 6 (3-6) p261-73, ISSN 0893-9675 Journal Code: 8914610
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A not yet understood phenomenon in carcinogenesis is the enormous difference in cancer susceptibility of **cells** from **different** species and of **cells** from individuals within the same species but with **different** age. **Reviewing** of the literature points to the promotion phase as the key for this difference. The essence of promotion appears to be a profound switch in the **cell** functions that enable **cells** to respond to stresses such as those caused by wounds and infection (**cell** activation). It was suggested that this switch involves an increase in the life span of the **cells** which, in turn, may predispose them to **immortalization**. A relationship of this switch with the onset of genetic instability was suggested, but it is not clear whether genetic instability is inherent to this switch or due to an incorrect performance of either switching on or switching off the response. The cause of species and age-specific differences in cancer susceptibility has therefore been sought in species and age-specific differences on the regulatory control of **cell** activation, an area that is still largely a black box.

6/3,AB/43 (Item 43 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09138599 97050763 PMID: 8895502
Tumour suppressive properties of the adenovirus 5 E1A oncogene.
Mymryk J S
Department of Pharmacology & Toxicology, The University of Western Ontario, London Regional Cancer Centre, Canada.
Oncogene (ENGLAND) Oct 17 1996, 13 (8) p1581-9, ISSN 0950-9232 Journal Code: 8711562
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The transforming oncogenes of DNA tumour viruses have proven useful as

tools to dissect the mechanisms of complex **cellular** processes. In particular, studies of the multifunctional proteins encoded by the early region 1A (E1A) of human adenovirus types 2 and 5 have provided insight into the regulation of **cellular** gene expression, growth and **differentiation**. Despite their well known ability to **immortalize** primary rodent **cells** and transform them in cooperation with a second oncogene, the E1A proteins also exhibit significant anti-tumour/tumour suppressive activity. This **review** focuses on the surprising ability of E1A to function as a tumour suppressor gene.

6/3,AB/44 (Item 44 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08940273 96289093 PMID: 8764138
Plasticity in epithelial polarity of renal intercalated **cells**: targeting of the H(+)-ATPase and band 3.
Al-Awqati Q
College of Physicians and Surgeons of Columbia University, New York, New York 10032, USA.
American journal of physiology (UNITED STATES) Jun 1996, 270 (6 Pt 1) pC1571-80, ISSN 0002-9513 Journal Code: 0370511
Contract/Grant No.: DK-20999; DK; NIDDK
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The intercalated **cell** is an epithelial **cell** of the renal collecting tubule that is specialized for H+ and HCO3- transport. These **cells** exist as two types, alpha and beta. The alpha-**cell** secretes H+ into the lumen by an apical H(+)-ATPase and a basolateral Cl-/HCO3- exchanger that is a form of band 3 protein (AE1). The beta-**cell** secretes HCO3- into the lumen by an apical Cl-/HCO3- exchanger and a basolateral H(+)-ATPase. In a previous study, it was suggested that a reversal in epithelial polarity of these **cells** occurs during the response of the kidney to an acid load (G.J. Schwartz, J. Barasch, and Q. Al-Awqati. Nature Lond. 318: 368-371, 1985). Recent studies, however have shown that there are many other subtypes where the distribution of these two proteins does not fit into this neat bipolar classification. This group of investigators recently generated an **immortalized cell** line of the beta-intercalated **cell** and found that the apical Cl-/HCO3- exchanger is also AE1. Furthermore, when these **cells** were seeded at high densities, the polarized targeting of the apical band 3 was reversed to the basolateral membrane. This was produced by the secretion of extracellular matrix protein that by themselves were capable of reversing the polarity of band 3 (J. S. van Adelsberg, J. C. Edwards, J. Takito, B. Kiss, and Q. Al-Awqati. **Cell** 76: 1053-1061, 1995). A large new extracellular matrix protein, hensin, was identified and found to be present exclusively in the collecting tubule. The extensive recent literature on the biology of alpha- and beta-intercalated **cells** is **reviewed** here and found to be compatible with the idea of the reversal of polarity as a mechanism for the regulation of H+ secretion by the tubule.

6/3,AB/45 (Item 45 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08711769 96063036 PMID: 7576308
Transgenic targeting of neuroendocrine peptide genes in the hypothalamic-pituitary axis.
Waschek J A
Department of Psychiatry, University of California, Los Angeles

90024-1759, USA.
Molecular neurobiology (UNITED STATES) Apr-Jun 1995, 10 (2-3) p205-17, ISSN 0893-7648 Journal Code: 8900963
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A large number of neuroendocrine peptide genes have been tested for their ability to target expression to the hypothalamus and pituitary in transgenic mice. This has resulted in a number of powerful applications, for example, ablation or **immortalization** of specific **cell** types, and analysis of transcription regulatory sequences. The greatest amount of success in targeting **cells** of the neuroendocrine axis has been in the pituitary and has utilized regulatory sequences of genes that are normally expressed in pituitary. Greater difficulties have been encountered in directing expression to specific neurons in the hypothalamus. A primary goal of this **review** is to consider collectively the data obtained by a number of laboratories in order to draw conclusions about the general sequence requirements for achieving **cell** -specific expression. The data suggest that the mechanisms controlling **cell** -specific expression of neuropeptide genes in the hypothalamus are complex and involve multiple regulatory elements that may reside within the gene or many kilobases away from the promoter. These elements act positively and negatively in **different cells** to enhance or restrict expression, and may include sequences that shield a transgene from regulatory influences of other genes near the point of chromosomal insertion.

6/3,AB/46 (Item 46 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08625950 95384203 PMID: 7655511
The H-2KbtsA58 transgenic mouse: a new tool for the rapid generation of novel **cell** lines.
Noble M; Groves A K; Ataliotis P; Ikram Z; Jat P S
Ludwig Institute for Cancer Research, London, UK.
Transgenic research (ENGLAND) Jul 1995, 4 (4) p215-25, ISSN 0962-8819 Journal Code: 9209120
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The ability to generate expanded populations of individual **cell** types able to undergo normal **differentiation** in vitro and in vivo is of critical importance in the investigation of the mechanisms that underly **differentiation** and in studies on the use of **cell** transplantation to repair damaged tissues. This **review** discusses the development of a strain of transgenic mice that allows the direct derivation of conditionally **immortal cell** lines from a variety of tissues, simply by dissociation of the tissue of interest and growth of **cells** in appropriate conditions. In these mice the tsA58 mutant of SV40 large T antigen is controlled by the interferon-inducible Class I antigen promoter. **Cells** can be grown for extended periods in vitro simply by growing them at 33 degrees C in the presence of interferon, while still retaining the capacity to undergo normal **differentiation** in vivo and in vitro. In addition, it appears that **cell** lines expressing mutant phenotypes can readily be generated by preparing cultures from appropriate offspring of matings between H-2KbtsA58 transgenic mice and mutant mice of interest.

6/3,AB/47 (Item 47 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08294677 95052813 PMID: 7963688
Approaches to gene transfer in keratinocytes.
Fenjves E S
Department of Oral Biology and Pathology, School of Dental Medicine, State University of New York, Stony Brook 11794-8702.
Journal of investigative dermatology (UNITED STATES) Nov 1994, 103 (5 Suppl) p70S-75S, ISSN 0022-202X Journal Code: 0426720
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The introduction and expression of exogenous genetic material in cultured **cells** has provided a powerful tool for studying gene function and regulation. **Immortalized cell** lines have been useful for establishing gene transfer methodologies that are generally inefficient. For investigators of epidermal and mucosal biology, wishing to make use of the tissue architecture produced by primary keratinocytes in vitro, the limited life span of these **cells** presents a host of unique problems. Primary **cells** require the use of gene transfer methods that are highly efficient and will not significantly alter the **cell**'s normal **differentiation** pathway. The purpose of this **review** is to evaluate gene transfer technology as it applies to keratinocytes.

6/3,AB/48 (Item 48 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07951095 94093808 PMID: 1341946
From chance to choice in the generation of neural **cell** lines.
Noble M; Groves A K; Ataliotis P; Jat P S
Ludwig Institute for Cancer Research, Middlesex Hospital/University College Branch, London, England.
Brain pathology (Zurich, Switzerland) (SWITZERLAND) Jan 1992, 2 (1) p39-46, ISSN 1015-6305 Journal Code: 9216781
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Despite the central importance of **cell** lines in contemporary studies in **cellular** and molecular biology, many areas of potential investigation remain impeded by the limited number of lines available and by the difficulty in generating new lines of interest. Thus, there has been a constant pressure to develop improved methods for obtaining **cell** lines of particular interest. This **review** examines some of the problems associated with in vitro approaches to **cell** line generation. In addition, two **different** ways in which transgenic animals can be used to overcome the limitations of in vitro production of **cell** lines are discussed. In the first approach, specific promoters are utilized to target expression of **immortalizing** genes to **cells** of interest. The second approach is concerned with development of a strain of transgenic animals (the H-2KbtsA58 transgenic mouse) designed to obviate the need for identification of **cell** -type specific promoters, and in which it is theoretically possible to directly generate conditionally **immortal cell** lines from any tissue of the body by simple dissection and growth of **cells** in appropriate tissue culture conditions. Finally, approaches are also discussed in which investigations on the control of precursor **differentiation** have been applied so as to bypass the need for expression of activated **immortalizing** oncogenes in the generation of large quantities of conditionally **immortalized cells** with the capacity to undergo normal **differentiation** in vitro and in vivo.

6/3,AB/49 (Item 49 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

07879144 94017240 PMID: 8411705
[Advances in molecular genetics of the Niemann-Pick group of diseases]
Ohno K
Departmet of Neurobiology, School of Life Sciences, Faculty of Medicine, Tottori University.
Nippon rinsho. Japanese journal of clinical medicine (JAPAN) Sep 1993, 51 (9) p2293-9, ISSN 0047-1852 Journal Code: 0420546
Document type: Journal Article; Review; Review Literature ; English Abstract
Languages: JAPANESE
Main Citation Owner: NLM
Record type: Completed
Recent advances in molecular genetics of the Niemann-Pick group of diseases are **reviewed** . Types A and B Niemann-Pick disease are characterized by a deficiency of one of lysosomal hydrolases, i.e. acid sphingomyelinase. The enzyme was partially purified from a large amount of urine and the cDNA clones, encoding acid sphingomyelinase, were cloned. The gene encoding the enzyme has been localized at the region p 15.1-p 15.4 of chromosome 11 by analysis of a somatic **cell** hybrid and in situ hybridization. Several mutations, causing deficient sphingomyelinase activity, were identified among patients with **different** ethnic backgrounds. The expression experiments revealed that the mutations responsible for type A cause no detectable residual enzyme activities, while mutations responsible for type B, cause relatively higher residual enzyme activity of 2% to 40 %. Biochemical abnormalities in Type C Niemann-Pick fibroblasts are characterized by normal acid sphingomyelinase activity, accumulation of intracellular cholesterol and defective esterification of exogenously added cholesterol. The basic defect is still unknown. Similar abnormalities were observed in mutant mouse strains, BALB/c and C57 BL/Ks. The mutant C57BL/Ks mouse, which was found in Japan, has been characterized as a sphingomyelinosis and the genetic locus, spm, has been assigned to chromosome 18. By transferring a single human chromosome to the **immortalized cell** line, we have found human chromosome 18 can reduce intracellular cholesterol accumulation. More recently, Pentchev and co-workers found linkage of type C to human chromosome 18. It is highly probable that the spm and human type C mutations involve the same gene. Molecular cloning of the defective gene in muman and mouse mutation become practically possible.

6/3,AB/50 (Item 50 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07823952 93356457 PMID: 8352534
Oncogenes in **cellular** **immortalisation** and **differentiation** (**review**).
Gonos E S; Spandidos D A
Ludwig Institute for Cancer Research, London, U.K.
Anticancer research (GREECE) Jul-Aug 1993, 13 (4) p1117-22, ISSN 0250-7005 Journal Code: 8102988
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Oncogenes have been shown to be able to overcome the limited proliferative capacity of normal mammalian **cells** in culture enforcing them to an **immortalised** phenotype, which in turn may act as a primary step in tumourigenesis. The oncogenes which display such **immortalisation** activity have the common feature of nuclear localisation, while the oncogenes which are capable of transforming **cells** are mainly cytoplasmic. Oncogenes from both families have been shown to interfere with the **differentiation** processes of several

cell types. There is evidence that some of these proto-oncogenes may function as regulators of normal **cell differentiation**, and when **immortalisation** occurs this is a process of blocking the **cell** from achieving a **differentiated** state. This article focuses on the ability of some oncogenes with **different** functions, such as myc and ras, to override the limited **cellular** proliferative capacity and their effects on **differentiation** ; finally it examines the recent implications that some onco-suppressor genes are actively participating in **cellular differentiation** processes.

6/3,AB/51 (Item 51 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07637154 93155553 PMID: 8381452
Regulation of hepatic secretion of apolipoprotein B-containing lipoproteins: information obtained from cultured liver **cells**.
Dixon J L; Ginsberg H N
Department of Food Science and Human Nutrition, University of Missouri, Columbia 65211.
Journal of lipid research (UNITED STATES) Feb 1993, 34 (2) p167-79, ISSN 0022-2275 Journal Code: 0376606
Contract/Grant No.: H1-47586; PHS; HL-21006; HL; NHLBI; HL-36000; HL; NHLBI
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A major theme of this **review** is that apoB secretion is regulated post-translationally, and that apoB secretion reacts rapidly to the current state of lipid metabolism in the **cell**. Therefore, as discussed by Fungwe et al. (122), the metabolism of triglyceride and of cholesteryl ester, in so far as both can be used as core lipids for apoB-containing LPs, are inextricably linked, and the shortage of one or both of these lipids could, by "allowing" increased intracellular degradation in the ER, inhibit the secretion of apoB. Another theme in this **review** is that the regulation of apoB secretion may be quite **different** in rat hepatocytes compared to cultured **cells** (HepG2) used as a model for human hepatocytes. Exogenous fatty acids appear to modulate the rate of apoB secretion in HepG2 **cells**, whereas they have only minimal effects on apoB secretion in rat hepatocytes or liver. Increased dietary cholesterol, on the other hand, appears to be an important modulator of apoB secretion in rats, but the evidence for effects of cholesterol on apoB secretion in HepG2 **cells** is less convincing. Finally, because HepG2 **cells** are an **immortalized cell** line, there could be many differences between these **cells** and human hepatocytes in vivo. Therefore, many of the results obtained with HepG2 **cells** should be corroborated in primary cultures of human hepatocytes. However, investigators utilizing primary human hepatocytes should be sure that the culture conditions are adequate to maintain the continued transcription of liver specific genes and to prevent the dedifferentiation of these **cells** in culture (85, 86).

6/3,AB/52 (Item 52 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07555695 93082677 PMID: 1451111
The interaction of the erythropoietin receptor and gp55.
D'Andrea A D
Division of Pediatric Oncology, Dana-Farber Cancer Institute, Children's Hospital, Harvard Medical School, Boston, Massachusetts 02115.
Cancer surveys (UNITED STATES) 1992, 15 p19-36, ISSN 0261-2429 Journal Code: 8218015

Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Friend virus induced erythroleukaemia can be conveniently divided into a first stage and a second stage. The first stage results from the mitogenic stimulation of EPO-R by gp55. In the second stage, multiple proviral integrations appear to result in further transformation of the SFFV infected erythroblast to a leukaemogenic state. The first stage results from EPO-R activation. After retroviral entry, mediated through an unknown receptor, and after cDNA synthesis and proviral integration, viral proteins are synthesized. Gp55 binds and activates EPO-R. A small but measurable amount of gp55-EPO-R complex is transported to the **cell** surface (Casadewall et al, 1991). In the presence of helper virus, the defective SFFV genome is packaged and released for subsequent rounds of infection. During the first stage, erythroblasts proliferate but are not tumorigenic. During the second stage of Friend disease, subsequent infections result in further proviral integrations in the host genome. Some of these integrations result in increased Spi-1 expression, whereas others result in decreased p53 expression. These events appear to account for the leukaemogenic properties of **cells** at this stage, 4-6 weeks after the initial SFFV infection. The interaction between EPO-R and gp55 persists at this later stage, although its contribution to the malignant phenotype of the MEL **cells** is not known. The sequence of events during stage 1 and stage 2 does not appear to have absolute requirements. Starting with IL-3 dependent **immortalized** Ba/F3 **cells** , which already have some unknown proliferative mutation (Mathey-Prevot et al, 1986), gp55 and EPO-R can subsequently be introduced, resulting in tumorigenicity (Li et al, 1990). The primary focus of this **review** has been the early mitogenic stage of Friend disease. Several concepts have emerged regarding the interaction between gp55 and EPO-R. The interaction between the polypeptides is highly specific, occurs in the extracytoplasmic regions and the transmembrane region of the polypeptides and occurs within the same **cell**, not via **cell-cell** contact. Both EPO and gp55 activate EPO-R, via **different** binding sites, resulting in increased **cellular** tyrosine kinase activity. The first stage of Friend disease is an example of how a non-oncogene bearing retrovirus can induce leukaemia. The env gene of the SFFV is not a classical oncogene. It does not appear to be derived from a normal **cellular** proto-oncogene. The interaction of gp55 and EPO-R therefore supports the "receptor mediated leukaemogenesis" hypothesis (McGrath and Weissman, 1978, 1979).(ABSTRACT TRUNCATED AT 400 WORDS)

6/3,AB/53 (Item 53 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07378403 92314073 PMID: 1616956
Biochemical, immunological, and functional aspects of the growth-suppressor/oncoprotein p53.
Montenarh M
Department of Biochemistry, University of Ulm, Germany.
Critical reviews in oncogenesis (UNITED STATES) 1992, 3 (3) p233-56, ISSN 0893-9675 Journal Code: 8914610
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The **cellular** phosphoprotein p53 was initially discovered in a variety of in vitro transformed and tumor-derived **cell** lines. Later on, p53 was also found in normal, nontransformed **cells** albeit at very low levels. Inhibition of p53 functions by microinjection of anti-p53 antibodies prevented quiescent **cells** from reentering the **cell** cycle after serum stimulation, indicating that p53 might somehow be

involved in the regulation of **cell** proliferation. After detection of p53-specific mRNAs, the gene was discovered in diverse species ranging from fish and frog to man. Knowing the p53 DNA sequence, it became clear that mutant forms of p53 had **immortalizing** and, in cooperation with other oncogenes, transforming activities. On the other hand, wild-type p53 could suppress oncogene-mediated transformation. It seems clear now that wild-type p53 is a tumor suppressor. Moreover, analysis of p53 from many types of human tumors indicates that the p53 gene is a very frequent target for mutational alterations. Because the biochemical consequences of these alterations are not yet clear, it is not understood yet on the molecular level how p53 can act as an oncogenic protein, on one hand, and as a growth-suppressor protein on the other hand. Therefore, the present **review** aims to summarize the biochemical and immunological properties of p53 and to address some biological activities of p53 in order to allow more insight into how p53 might be regulated within the **cell** or how p53 might regulate **cell** proliferation.

6/3,AB/54 (Item 54 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07263239 92199443 PMID: 1802111
Cell cycle-regulated and proliferation stimulus-responsive genes.
Hofbauer R; Denhardt D T
Institut fur Molekularbiologie, Universitat Wein, Vienna, Austria.
Critical reviews in eukaryotic gene expression (UNITED STATES) 1991, 1 (4) p247-300, ISSN 1045-4403 Journal Code: 9007261
Contract/Grant No.: AG07972; AG; NIA
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

We have **reviewed** here genes whose expression may vary during the " **cell** cycle" and we discuss the underlying regulatory mechanisms. Given a correlation between the **cell** cycle and expression of a particular gene, the question arises whether that gene regulates the cycle, whether the cycle regulates that gene, or whether the correlation is simply the consequence that both the **cell** cycle and that gene respond to the same signal(s). Gene expression is regulated at diverse levels, and the relative importance of regulation at these **different** levels depends on which version of the **cell** cycle one has in mind; depending upon the context, the concept of the (higher eukaryote) **cell** cycle has a number of **different** operational meanings. Thus the first few divisions of the fertilized egg consist of successive S and M phases, with insignificant G1 and G2 phases, regulated entirely at the translational and post-translational level by the phosphorylation/dephosphorylation of p34cdc2 and the synthesis/degradation of one or more cyclins-keyed perhaps to the cytoplasm/nucleoplasm ratio and the completion of DNA replication. In contrast, **cells** stimulated to exit quiescence, (G0), require new gene transcription and changes in the post-transcriptional control of gene expression. **Cells** proliferating in a constant environment proceed directly from mitosis into G1 and are less dependent on (but not independent of) new transcription; here controls at the post-transcriptional and post-translational levels are more pronounced. In addition to regulation by p34cdc2, input from **cell**-specific growth factors or other extracellular signals is essential for most untransformed **cells** to continue through the cycle. Many transformed **cells** in contrast do not require exogenous signals and are altered in the way that key regulatory genes (e.g., p53, RB) are controlled. While **cells** of many lower eukaryotes appear capable of an indefinite number of **cell** cycles, the typical higher eukaryotic **cell** appears to have a limit on this number--untransformed, nonestablished vertebrate **cells** are usually mortal. For unknown reasons, established **cell** lines and certain embryonic or stem **cells** under the right conditions, are

immortal and capable of indefinite proliferation. Apparently, the price paid to construct a **differentiated** multicellular organism is a limit on the number of **cell** divisions that the constituent somatic **cells** are capable of undergoing.

6/3,AB/55 (Item 55 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07252727 92182174 PMID: 1311965
Early-stage squamous **cell** and adenocarcinoma of the cervix.
McGonigle K F; Berek J S
University of California, Los Angeles School of Medicine.
Current opinion in obstetrics & gynecology (UNITED STATES) Feb 1992, 4 (1) p109-19, ISSN 1040-872X Journal Code: 9007264
Document type: Journal Article; Review; Review Literature
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Articles on early-stage squamous **cell** and adenocarcinoma of the cervix published between August 1990 and July 1991 are **reviewed**. A new monoclonal antibody used to distinguish endocervical from endometrial **differentiation** is described, as well as a histochemical means of distinguishing in situ from invasive adenocarcinoma. In vitro and in vivo studies of **cell** lines **immortalized** with human papillomavirus DNA are described with a discussion of the mechanism of the development of malignancy. An animal model to test and develop an anti-human papillomavirus vaccine is presented. The epidemiology of adenocarcinoma is also **reviewed** , and the development of invasive carcinoma after conservative therapy or conization for dysplasia is discussed. Computed tomography scanning has been found to be no more accurate than examination for staging of early cervical cancer. Several studies in the **review** period have evaluated risk factors for recurrent disease in patients treated for early-stage cervical cancer, including a prospective surgical pathologic study by the Gynecologic Oncology Group. The optimal treatment of early stage I adenocarcinoma of the cervix is discussed, comparing the efficacy of primary surgical therapy with the efficacy of radiation therapy. The risk of ovarian metastases in patients with early-stage cervical cancer is very low for both squamous **cell** and adenocarcinoma. The surgical technique and efficacy of laparoscopic pelvic lymphadenectomy for patients with early-stage cervical cancer are discussed. Lateral transposition of the ovaries at the time of radical hysterectomy for cervical cancer has significant potential benefits but also risks. Finally, surveillance methods that detect recurrent cervical cancer after treatment for early-stage disease are discussed.

6/3,AB/56 (Item 56 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06758346 91069058 PMID: 2174661
Genetic strategies of tumor suppression.
Sager R
Department of Microbiology and Molecular Genetics, Harvard Medical School, Boston, MA.
American review of respiratory disease (UNITED STATES) Dec 1990, 142 (6 Pt 2) pS40-3, ISSN 0003-0805 Journal Code: 0370523
Contract/Grant No.: CA-39814; CA; NCI
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The evaluation of the cancer **cell** is a complex multigene process. Tumor suppressor genes that are lost or inactivated, as well as genes that

are overexpressed, play key roles in tumor progression. The identification of overexpressed genes has been expedited by the presence of transforming genes in some animal retroviruses. However, tumor suppressor genes have been difficult to identify and isolate because of their loss or inactivation during tumorigenesis. By a variety of methods, summarized in this **review** , a few tumor suppressors have been cloned and characterized, and many more have been recognized indirectly. The general finding at this time is that the same tumor suppressors (and oncogenes) are found associated with many **different** tumors, that several **different** altered genes are found typically in the same tumors, and that other oncogenes and tumor suppressor genes seem to be characteristically altered in particular tumor types as well. Functions of tumor suppressor genes include the control of normal **cell** activities such as proliferation and **differentiation** as well as senescence, which is a special kind of **differentiation** in which **cells** lose their ability to divide. The genetic basis of senescence and identification of genes involved in overcoming senescence, leading to **immortalization** (i.e., indefinite growth potential), are important areas of current investigation. Our laboratory is engaged in senescence/ **immortalization** studies as a result of our discovery that normal human mammary epithelial **cells** can be **immortalized** by DNA of the human papilloma virus. These new studies are summarized here.

6/3,AB/57 (Item 57 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06740479 91053038 PMID: 2241098
Colorectal carcinogenesis: sequential steps in the in vitro **immortalization** and transformation of human colonic epithelial **cells** (**review**).
Paraskeva C; Corfield A P; Harper S; Hague A; Audcent K; Williams A C
Department of Pathology, University of Bristol, Medical School, U.K.
Anticancer research (GREECE) Sep-Oct 1990, 10 (5A) p1189-200, ISSN 0250-7005 Journal Code: 8102988
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The development of colorectal cancer is an excellent example of the complex multistage nature of carcinogenesis and most colorectal cancers are thought to develop from adenomas. In this paper we have **reviewed** in vitro models developed in our laboratory for the study of human colorectal carcinogenesis. For these studies epithelial **cell** lines have been isolated from hereditary and sporadic colorectal adenomas representing **different** stages in tumour progression. Karyotypic analysis has shown specific abnormalities of chromosomes 1, 7, 14, 17, 18 and 22 to occur in these premalignant adenoma **cell** lines. The majority of **cell** cultures derived from small adenomas (less than 1 cm in diameter) senesced whereas the larger adenomas (greater than 2 cm in diameter) were more likely to give rise to **immortal cell** lines indicating that the acquisition of in vitro **immortality** occurs at a relatively late stage of colorectal carcinogenesis. Abnormalities of chromosome I have been implicated in tumour progression and in the in vitro **immortalization** of colorectal adenomas. Furthermore, several stages have been described in the transformation of an adenoma **cell** line PC/AA to a tumorigenic phenotype. Sodium butyrate and the potent carcinogen N-methyl-N-nitro-nitrosoguanidine (MNNG) were used in this transformation. Sodium butyrate is proposed to act as a possible promoter of colorectal carcinogenesis, and MNNG to cause the further genetic changes required for the conversion of the premalignant **cells** to a carcinoma. Markers to study the progression of an adenoma **cell** line to a tumorigenic phenotype in vitro include in vitro **immortalization**, aneuploidy, clonogenicity, resistance to the inhibitory effects of sodium butyrate,

anchorage independent growth, ras gene activation, production of active proteinases and tumorigenicity in athymic nude mice. A role for a constitutively produced tumour promoter in colorectal carcinogenesis is discussed together with the possibility that **different** events are involved in the development of sporadic versus hereditary tumours due to the importance of the microenvironment in hereditary cancer. Our in vitro progression provides the first experimental evidence for the adenoma to carcinoma sequence and the cytogenetic evidence suggests that it is relevant to in vivo carcinogenesis.

6/3,AB/58 (Item 58 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06196636 89281014 PMID: 2543878
Expression of membrane receptors and (proto)oncogenes during the ontogenic development and neoplastic transformation of the intestinal mucosa.
Chastre E; Emami S; Gespach C
INSERM U.55, Unite de Recherches sur les Peptides Neurodigestifs et le Diabete, Hopital Saint-Antoine, Paris, France.
Life sciences (ENGLAND) 1989, 44 (23) p1721-42, ISSN 0024-3205 Journal Code: 0375521
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The functional relationship between membrane receptors involved in signal transduction and (proto) oncogene expression has been explored during the ontogenic development and **differentiation** of the intestinal mucosa in man and rat. The present **review** develops detailed picture of the current understanding of some mechanisms underlying growth and function of normal, **immortalized** and cancerous intestinal epithelial **cells**.

6/3,AB/59 (Item 59 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06066893 89152553 PMID: 3068018 Record Identifier: 89152553
Diversity of the osteoblastic phenotype.
Rodan G A; Heath J K; Yoon K; Noda M; Rodan S B
Department of Bone Biology, Merck Sharp and Dohme Research Laboratories, West Point, Pennsylvania 19486.
Ciba Foundation symposium (NETHERLANDS) 1988, 136 p78-91, ISSN 0300-5208 Journal Code: 0356636
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Other Citation Owner: NASA
Record type: Completed
Studies of bone **cells** in culture have raised two salient questions: are the findings representative of the in vivo situation and can the conflicting data from **different** **cell** models be reconciled? **Review** of the literature indicates that all osteoblastic **cells**, defined by their origin or by their ability to produce mineralized matrix, have a few common properties: production of type I collagen; increased alkaline phosphatase activity; and parathyroid hormone-stimulated adenylate cyclase. Other features, such as osteocalcin and prostaglandin E production and the response to prostaglandin E, are selectively expressed by certain **cell** types. Pilot studies on mRNA levels of 'bone proteins' in developing calvaria suggest that such differences may reflect stages in osteoblastic **differentiation**. **Immortalization** of calvaria-deriv ed **cells** using a SV40 large T antigen vector, which may freeze the **cells** in their particular state of **differentiation** (as proposed

for leukaemia **cells**), yields phenotypes consistent with that hypothesis. **Immortal cell** lines may thus help to characterize osteoblastic **differentiation** . The diversity of osteoblast responses in culture to hormones and growth factors could be due to these phenotype differences but could also represent a subspecialization of **differentiated cells** . In addition, in the organism regulatory agents act in concert on a heterogeneous interactive **cell** population. Nonetheless **cell** cultures can be useful in screening for and predicting in vivo responses, as was shown by the 1,25-(OH)2D3 stimulation of osteocalcin, and for studying the molecular mechanisms of regulatory effects. **Cell** lines are also convenient for the production of specific proteins and cDNA libraries, and for the expression of specific genes.

6/3,AB/60 (Item 60 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05934372 89024505 PMID: 3052259
Onco-suppressor genes and their involvement in cancer (**review**).
Anderson M L; Spandidos D A
Department of Biochemistry, University of Glasgow, Scotland.
Anticancer research (GREECE) Sep-Oct 1988, 8 (5A) p873-9, ISSN 0250-7005 Journal Code: 8102988
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Onco-suppressor genes are a heterogeneous set of genes that inhibit the cancer-related phenotype of **cells** . Because they are difficult to identify, only a few have been described. Evidence for their existence has mainly been indirect and comes from the following types of study. 1. Recessive cancer genes in higher and lower eukaryotes have been detected. If both alleles of these genes are deleted or inactivated, cancer develops. 2. Studies on **cell** hybrids have implicated genes which suppress various stages in the malignant conversion of normal **cells** e.g. **immortalisation** , morphological conversion and metastasis. 3. The isolation from virally induced transformants of flat, non-tumorigenic revertants in which expression of the transforming gene is not down-regulated suggests the presence of genes which suppress the effects of transformation. 4. Blocks to **differentiation** can be bypassed by inducing compounds or **differentiation** factors. 5. Studies on tumor inhibitory factors such as tumour necrosis factor and beta-TGF show that they have **different** effects on **different** types of **cell** -acting to promote growth in some cases and inhibit it in others. 6. The discovery of cis-acting negatice regulatory elements suggests that interaction of such elements with proteins may be important for control of gene expression particularly of infecting oncogenic viruses. 7. Suppression of the transformed phenotype of malignant **cells** by contact with normal **cells** that controls growth of neighboring **cells**. 8. The inhibition of proliferation of transformed **cells** by transfection with DNA from normal **cells** may be a useful method for cloning onco-suppressor genes. We discuss what is known and what is not known about this important class of gene.

6/3,AB/61 (Item 61 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05783985 88208573 PMID: 3284497
Potential and limitations of cultivated fibroblasts in the study of senescence in animals. A **review** on the murine skin fibroblasts system.
Van Gansen P; Van Lerberghe N

Laboratoire de Cytologie et Embryologie moleculaires, Universite libre de Bruxelles, Rhode-Saint-Genese, Belgium.
Archives of gerontology and geriatrics (NETHERLANDS) Mar 1988, 7 (1) p31-74, ISSN 0167-4943 Journal Code: 8214379
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Senescence is the last period of the life span, leading to death. It happens in all animals, with the exception of a few didermic species (Hydras) having a stock of embryonic **cells** and being **immortal**.
The causes of animal senescence are badly known. They depend both on genetic characters (maximum life span of a species) and on medium factors (mean expectation of life of the animals of a species). Animal senescence could depend on **cell** aging: (1) by senescence and death of the **differentiated cells**, (2) by modified proliferation of the stem **cells** of **differentiated** tissues, (3) by alterations in the extracellular matrices, (4) by interactions between factors (1) (2) and (3) in each tissue, and (5) by interactions between the several tissues of an organism. This complexity badly impedes the experimental study of animal senescence. Normal mammal **cells** are aging when they are cultivated (in vitro aging). Present literature upon in vitro aging of cultivated human fibroblasts consists essentially of papers devoted to proliferation and **differentiation** characteristics and not to **cell** senescence.
Murine skin fibroblasts have been studied in our laboratory, using **different** systems: (1) primary cultures isolated from peeled skins of mouse embryos, (2) mouse derms analysed in the animals, (3) cultivated explants of skins, (4) serial sub-cultures of fibroblasts isolated from these explants, (5) **cells** cultivated comparably on plane substrates (glass, plastic, collagen films) and on three-dimensional matrices (collagen fibres). In primary cultures (system 1) all the **cell** generations have been analysed, including the last one until death of the culture. We have shown that many characters are varying with **cell** generation. All the observed variations were: progressive, non-linear and correlated (intracellular feedbacks). We come to the conclusion that the main effects of **cell** mitotic age are (1) to depress the plasticity of the chromatin, (2) to change the organization of the cytoplasmic filaments, (3) to change the organization of the extracellular matrix. The collagen fibres are also acting upon nucleus and filaments either in the animals or in the cultures. The phenotype of a fibroblastic **cell** is thus both age- and environment-dependent. Overall data on in vitro **cell** aging point to the hypothesis that senescent **cells** are phenotypic variants and not mutant **cells**. Aging **cell** cultures are remarkably useful to the studies on **cell** proliferation decrease and **cell** cycle lengthening shown by the stem **cells** in animal tissues. We propose the hypothesis that the fibroblasts of the vertebrates would be homologous to the pluripotent mesenchyme **cells** of their embryos.

6/3,AB/62 (Item 62 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05408261 87156950 PMID: 3030347
The Epstein-Barr virus genome and phenotypic expression during lytic cycle.
Pearson G R
AIDS research (UNITED STATES) Dec 1986, 2 Suppl 1 pS49-56, ISSN 0737-6006 Journal Code: 8310361
Contract/Grant No.: CA39617; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The Epstein-Barr Virus (EBV) has been studied extensively as a human

cancer virus. Until recently, however, little was known about the viral genes encoding for **different** proteins involved in the virus **immortalization** and replication cycles. Most of the efforts have been directed at those genes expressed in **immortalized cells**. However, more recently, there has also been advances in the mapping of genes encoding for polypeptides expressed in the virus replication cycle and in the characterization of the proteins encoded by these genes. The purpose of this article is to **review** some of these new developments in identifying viral genes and their products. In addition, the current status of the development of a subviral vaccine against this virus is discussed.

6/3,AB/63 (Item 63 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05364176 87118327 PMID: 3543942
Experimental models of bladder cancer: a critical **review**.
Raghavan D; Debruyne F; Herr H; Jocham D; Kakizoe T; Okajima E; Sandberg A; Tannock I
Progress in clinical and biological research (UNITED STATES) 1986, 221 p171-208, ISSN 0361-7742 Journal Code: 7605701
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We have **reviewed** critically the available models of bladder cancer,. and have attempted to compare their strengths and weaknesses where appropriate data are available. Further direct comparisons of the applications of each model will be needed in order to rank them, and to identify areas of research where each model will predominate. Furthermore, more information will be needed to validate each model in the context of human disease. With the increasing range and sophistication of the tools of molecular biology, a very important future direction will be the characterisation of animal and human bladder cancer, and in particular the study of the changes from normal to neoplastic urothelium: tumor markers, chromosomal patterns and oncogenes that are associated with specific biological functions, such as invasion, metastasis and ultimate prognosis. The transfection of normal tissues by oncogenes to yield transformed or **immortalised** lines may be of critical importance in identifying the nature of neoplastic transformation. The use of animal tumors and xenografts, each with the availability of a physiological internal milieu (although **different** from human metabolic conditions) may yield useful systems for the testing of new therapeutic approaches. However, of the utmost importance is the continuing need to characterise and validate each model, to avoid multiple publications and nomenclatures pertaining to common lines, and to recognise the limitations of the heavily adapted long term **cell** lines in vivo and in vitro. The major deficiencies of the available lines continue to be found in the method of their application to basic research, rather than being inherent in themselves. Although there are many theoretical and practical applications of these models, it should not be forgotten that the direct study of human bladder cancer, including the appropriate processing of biopsy specimens, will remain integral to understanding the biology of this disease.

6/3,AB/64 (Item 64 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04996474 86071229 PMID: 3878011
[Current developments in hybridoma technology]
Recente ontwikkelingen in de hybridomatechnologie.
Osterhaus A D; UytdeHaag A G
Tijdschrift voor diergeneeskunde (NETHERLANDS) Oct 15 1985, 110 (20)

p835-9, ISSN 0040-7453 Journal Code: 0031550
Document type: Journal Article ; English Abstract
Languages: DUTCH
Main Citation Owner: NLM
Record type: Completed
A **review** of recent developments in hybridoma technology is presented. The advantages and disadvantages of **different** methods of immunization, **immortalization** , selection and cultivation of hybridomas are evaluated. Recent and promising developments in the field of the application of monoclonal antibodies are discussed.

6/3,AB/65 (Item 65 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04810933 85190872 PMID: 3991734
Induction-dependent and lineage-dependent models for **cell** diversification are mutually exclusive.
Holtzer H; Biehl J; Holtzer S
Progress in clinical and biological research (UNITED STATES) 1985, 175 p3-11, ISSN 0361-7742 Journal Code: 7605701
Contract/Grant No.: CA-18194; CA; NCI; HL-15835; HL; NHLBI; HL-18708; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The purpose of this brief **review** is to put into perspective just how little is known about the mechanisms that control the assembly of the **differentiation** program of any **cell** type. Any number of "trivial" changes in the microenvironment of a Friend erythroleukemic or of a neuroblastoma **cell** induces both covertly **differentiated cells** to reveal their lineage affiliations. Demethylating molecules, BudR, retinoic acid, cAMP, butyrate or other "inducing molecules" do not, however, transform the descendents of the neuroblastoma **cell** into a Hb- synthesizing **cell** or vice versa. For thousands of generations both of these immortalized lines transmit to their daughters their unique, lineage-dependent **differentiation** programs with great fidelity. The stability of the inherited transcription complex that is ultimately responsible for this covert **differentiation** program of these **cell** lines--or of normal precursor **cells**--is awesome. Clearly, with these **immortalized cells** as with normal chick blastodisc **cells**, the **cell** 's microenvironment plays a major role in permitting or blocking the expression of the **cell**'s inherited **differentiation** program. But the program itself must be generated by intracellular mechanisms and must be inherited; its assembly is not dependent upon inductive events initiated by exogenous molecules.

6/3,AB/66 (Item 66 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04771670 85145246 PMID: 6084947
Human T-**cell** leukemia virus: its discovery and role in leukemogenesis and immunosuppression.
Shaw G M; Broder S; Essex M; Gallo R C
Advances in internal medicine (UNITED STATES) 1984, 30 p1-27, ISSN 0065-2822 Journal Code: 0370427
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We have highlighted the events leading to the discovery of the first human RNA tumor virus and then **reviewed** what is currently known about

haemopoietic stem **cell**.
Schofield R
Blood cells (GERMANY, WEST) 1978, 4 (1-2) p7-25, ISSN 0340-4684
Journal Code: 7513567
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Several experimental findings that are inconsistent with the view that the spleen colony-forming **cell** (CFU-S) is the primary haemopoietic stem **cell** are **reviewed**. Recovery of CFU-S, both quantitatively and qualitatively, can proceed **differently** depending upon the cytotoxic agent or regime used to bring about the depletion. The virtual **immortality** of the stem **cell** population is at variance with evidence that the CFU-S population has an 'age-structure' which has been invoked by several workers to explain experimental and clinical observations. To account for these inconsistencies, a hypothesis is proposed in which the stem **cell** is seen in association with other **cells** which determine its behaviour. It becomes essentially a fixed tissue **cell** . Its maturation is prevented and, as a result, its continued proliferation as a stem **cell** is assured. Its progeny, unless they can occupy a similar stem **cell** 'niche', are first generation colony-forming **cells** , which proliferate and mature to acquire a high probability of **differentiation**, i.e., they have an age-structure. Some of the experimental situations **reviewed** are discussed in relation to the proposed hypothesis.

6/3,AB/71 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13708846 BIOSIS NO.: 200200337667
Aging and survival of cutaneous microvasculature.
AUTHOR: Chang Edwin; Yang Jiwei; Nagavarapu Usha; Herron G Scott(a)
AUTHOR ADDRESS: (a)Department of Dermatology, Stanford University School of Medicine, Stanford, CA, 94305**USA E-Mail: gsherron@mmrx.org
JOURNAL: Journal of Investigative Dermatology 118 (5):p752-758 May, 2002
MEDIUM: print
ISSN: 0022-202X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The growth and turnover of blood vessels in the skin is fundamental in normal development, wound repair, hair follicle cycling, tumor **cell** metastasis, and in many **different** states of cutaneous pathology. Whereas many investigations are focused on mechanisms of angiogenesis in the skin, the influence of **cellular** aging and replicative senescence (i.e., the inability, after a critical number of population doublings, to replicate) on microvascular remodeling events has received relatively less attention. In this article, we **review** the clinical and pathologic relationships associated with cutaneous vascular aging and update current knowledge of endothelial **cell** survival characteristics. A hypothesis is presented in which endothelial **cell** aging and survival are linked to molecular mechanisms controlling **cell** proliferation, quiescence, apoptosis, and **cellular** senescence. We **review** recent results demonstrating how activation of telomerase in human dermal microvascular endothelial **cells** affects their durability both in vitro and in vivo and conclude by linking these studies with current concepts involving endothelial **cell** precursors, control of postnatal somatic **cell** telomerase activity, and murine model systems.

2002

6/3,AB/72 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13191118 BIOSIS NO.: 200100398267
Mammalian stem **cells** in vitro as a basis for the development of new biotechnologies.
AUTHOR: Lukash L L; Vasilovskaya S V
JOURNAL: Biopolimery i Kletka 17 (3):p203-211 May-June, 2001
MEDIUM: print
ISSN: 0233-7657
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: Ukrainian; Non-English
SUMMARY LANGUAGE: English; Ukrainian; Russian

ABSTRACT: In this **review** we considered the main directions of the research using stem **cells** of human and animals: the creation of **cellular** banks, an investigation of the properties of the polipotent stem **cells** and obtaining of **immortal cell** lines, a role of growth factors and cytokines in the **differentiation** of the stem **cells**, **cell** therapy as an alternative of organ transplantation, recapitulation of the embryogenesis and animal cloning.
2001

6/3,AB/73 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12137716 BIOSIS NO.: 199900432565
The molecular basis of **cell** cycle and growth control.
BOOK TITLE: The molecular basis of **cell** cycle and growth control
AUTHOR: Stein Gary S(a); Baserga Renato; Giordano Antonio; Denhardt David T
BOOK AUTHOR/EDITOR: Stein G S; Baserga R; Giordano A; Denhardt D T: Eds
AUTHOR ADDRESS: (a)Department of Cell Biology and Cancer Center, University of Massachusetts Medical Center, 55 Lake Avenue North, Worcester, MA, 01655**USA
px+389p 1999
BOOK PUBLISHER: Wiley-Liss, Inc., 605 Third Avenue, New York, New York 10158-0012, USA
Wiley-Liss, Ltd., Chichester, England
ISBN: 0-471-15706-6
DOCUMENT TYPE: Book
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: This text with nine chapters authored by an international team of scientists, **reviews** up-to-date information on the biochemical parameters and gene regulatory mechanisms that mediate **cell** growth control and **cell** cycle progression. The book begins with an introduction to the problem of **cell** cycle control, followed by chapters examining DNA replication and S phase, mitosis and meiosis, regulation of gene expression, growth factors and growth factor receptor-mediated pathways, signal transduction and integration of regulatory information, **differentiation**, development and programmed **cell** death, **cellular** senescence and **immortalization**, and antisense strategies in the treatment of cancers. Black-and-white and color illustrations, references at the end of each chapter, and a subject index accompany the work. Biomedical researchers; **cell**, molecular,

cancer, and developmental biologists; biochemists; molecular geneticists, oncologists, and pathologists; and immunologists are the intended audience for this volume.

1999

6/3,AB/74 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11351085 BIOSIS NO.: 199800132417
Mortality and **immortality** at the **cellular** level: A **review**

AUTHOR: Hayflick L(a)
AUTHOR ADDRESS: (a)Univ. Calif. San Francisco, P.O. Box 89, The Sea Ranch, CA 95497**USA
JOURNAL: Biochemistry (Moscow) 62 (11):p1180-1190 Nov., 1997
ISSN: 0006-2979
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A brief history of **cell** culture as it pertains to aging research had its origins with the thoughts of Weismann and the work of Carrel. Until the early 1960's it was believed that normal **cells** had an unlimited capacity to replicate. Consequently, aging was thought to have little to do with intracellular events. In the early 1960's we overthrew this dogma after finding that normal **cells** do have a finite replicative capacity. We interpreted this phenomenon to be aging at the **cellular** level. In subsequent years the objective was to identify the putative **cell** division counting mechanism that had been postulated to exist. Efforts to achieve this goal have had a remarkable degree of success only in the last few years with the discovery of the shortening of telomeres at each round of DNA replication that occurs in normal **cells** both in vivo and in vitro. **Immortal** abnormal **cell** populations overcome telomere shortening by activating an enzyme, telomerase, that catalyzes the synthesis of the TTAGGG sequences that compose mammalian telomeres, thus maintaining their length constant. Telomere shortening in normal **cells** is not a chronometer because time is not measured but rounds of DNA replication are measured. I propose the term replicometer for the device that measures the loss of telomeric sequences in normal **cells** because the action is that of a meter, and it is counting DNA replications. Telomere shortening and the finite lifetime of normal **cells** is more likely to represent longevity determination than it is aging. The hundreds of biological changes that herald the loss of replicative capacity in normal **cells** are more likely age changes.

1997

6/3,AB/75 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10716930 BIOSIS NO.: 199799338075
Resistance to cytotoxic treatments: A critical analysis.
AUTHOR: Vicente J(a); Lobo F; Domine M; Garcia-Estevez L
AUTHOR ADDRESS: (a)Servicio de Oncol., Fundacion Jimenez Diaz, Madrid** Spain
JOURNAL: Oncologia (Madrid) 19 (10):p27-36 1996
ISSN: 0378-4835
DOCUMENT TYPE: Literature Review

RECORD TYPE: Abstract
LANGUAGE: Spanish; Non-English
SUMMARY LANGUAGE: Spanish; English

ABSTRACT: Drug resistance is the main obstacle for success in cancer chemotherapy. Several mechanisms of biochemical resistance affecting single and particular drugs have been known since a long time. In addition, the most important mechanism of resistance, affecting many **different** drugs at the same time, has been discovered along the lost twenty years, the so-called pleiotropic resistance. This is due in small proportion to DNA-topoisomerase II alterations, but mainly to the **cell** expression of MDR1 and MRP surface proteins, that behave as true extrusion pumps for natural toxic substances and are **reviewed** with some detail in the text. Biochemical resistance is an evolutive process of spontaneous genetic mutation, the rate of which fluctuates according to that of each **cellular** clone. The mathematical model of Goldie and Coldman, formulated to relate the drug sensitivity of tumors to their spontaneous mutation rate, and their proposal of 'alternating' chemotheraphy, have not met practical success, perhaps due to the unequal effectiveness of the available alternating drug regimens. Day's worst drug rule, implying the most extensive use of the less effective combination, could be an excellent way to improve results, specially with the help of computer software carefully filled with real data. Many times, tumor resistance to chemotherapy is not genetic in origin, but depends on the proliferative status of its **cell** population, as shown by Norton and Simon almost twenty years ago. Tumor growth is actually gompertzian and chemosensitivity is maximal at the transition point, when growth rate is almost exponential, decreasing clearly and progressively at later positions and, most importantly, at much earlier situations. This emphasizes the intrinsic difficulty and decreasing ability of a particular treatment for killing the lost few tumor **cells**, that is very significant for adjuvant chemotherapy planning, making necessary its intensification precisely at the end of treatment. This is the actual basis of the present intensification chemotherapy with autologous or allogenic rescue, the results of which seem very promising. Furthermore, the progress against resistance to cytotoxic chemotherapy is already advancing at many tronts, mainly at the pharmacological version of pleiotropic resistance, at the temporal inhibition of bone marrow proliferation during chemotherapy, and at the molecular level. The molecular approaches comprise not only the modulation of proliferation signals and pathaways or the use of antisense oligonucleotides, but specifically directed chemotherapy and the transfer of suicide genes to tumor **cells** to driscriminate of suicide genes to tumor **cells** to discriminate killing or, inversely, of resistance genes to one marrow to avoid toxicity.

1996

6/3,AB/76 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07994719 BIOSIS NO.: 000093050392
THE F9-EC **CELL** LINE AS A MODEL FOR THE ANALYSIS OF **DIFFERENTIATION**
AUTHOR: ALONSO A; BREUER B; STEUER B; FISCHER J
AUTHOR ADDRESS: DEUTSCHES KREBSFORSCHUNGSZENTRUM, IM NEUENHEIMER FELD-280, D-6900 HEIDELBERG 1, GERMANY.
JOURNAL: INT J DEV BIOL 35 (4). 1991. 389-398. 1991
FULL JOURNAL NAME: International Journal of Developmental Biology
CODEN: IJDBE
DOCUMENT TYPE: Review
RECORD TYPE: Abstract

LANGUAGE: ENGLISH

ABSTRACT: The teratocarcinoma stem **cell** line F9 has been widely used as a model for the analysis of molecular mechanisms associated with **differentiation**. This **cell** line has been considered to be nullipotent and able to **differentiate** into endodermal-like derivatives upon treatment with retinoic acid. Nevertheless, under definite culture conditions, F9 **cells** are able to **differentiate** into derivatives of all three germ layers. The F9 **cells** express characteristics of early mouse embryonal **cells** and possess all repression factors known to be present in **cells** of the early mouse embryogenesis. Induction of **differentiation** can be achieved not only by adding chemical agents to the culture medium but also by transfection of several oncogenic sequences. In somatic **cell** genetic experiments, **immortalized, differentiated** F9-like **cells** have been shown to express dominantly genes responsible for the appearance of the **differentiated** phenotype.

1991

6/3,AB/77 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07485418 BIOSIS NO.: 000040054432
IMMORTALIZATION AND MALIGNANT TRANSFORMATION OF **DIFFERENTIATED CELLS** BY ONCOGENES IN-VITRO AND IN TRANSGENIC MICE
AUTHOR: PAUL D; SCHMIDT G H
AUTHOR ADDRESS: DEP. CELL BIOL., FRAUNHOFER INST. TOXICOL., HANNOVER, FRG.
JOURNAL: CRIT REV ONCOG 1 (3). 1989. 307-322. 1989
CODEN: CRONE
DOCUMENT TYPE: Review
RECORD TYPE: Citation
LANGUAGE: ENGLISH
1989

6/3,AB/78 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

06828777 BIOSIS NO.: 000038001001
DIFFERENTIATED MAMMALIAN **CELL** LINES **IMMORTALIZED** BY TEMPERATURE-SENSITIVE TUMOR VIRUSES
AUTHOR: CHOU Y J
AUTHOR ADDRESS: NAT. INST. CHILD HEALTH HUMAN DEV., NATL. INST. HEALTH, BUILDING 10, ROOM 8C429, BETHESDA, MD. 20892.
JOURNAL: MOL ENDOCRINOL 3 (10). 1989. 1511-1514. 1989
FULL JOURNAL NAME: Molecular Endocrinology
CODEN: MOENE
DOCUMENT TYPE: Review
RECORD TYPE: Citation
LANGUAGE: ENGLISH
1989

6/3,AB/79 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

03594266 BIOSIS NO.: 000074009843
IMMORTALITY OF THE GERM LINE GENETIC AND BIOCHEMICAL MECHANISMS A **REVIEW**

AUTHOR: MEDVEDEV Z A
AUTHOR ADDRESS: DIV. OF GENETICS, NATIONAL INST. FOR MED. RES., MILL HILL, LONDON, NW7 1AA GREAT BRITAIN .
JOURNAL: MECH AGEING DEV 17 (4). 1981 (RECD. 1982). 331-360. 1981
FULL JOURNAL NAME: Mechanisms of Ageing and Development
CODEN: MAGDA
DOCUMENT TYPE: Review
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The nature of the differences between mortal somatic **cells** and **immortal** germ **cell** lines constitutes a major area of theoretical gerontology which has not yet received adequate attention. Weismann's theory, first stated almost exactly a century ago, was recently reconsidered by Kirkwood and Holliday. They applied modern concepts and findings on the factors regulating the accuracy of synthesis of macromolecules to explain germ line **immortality**. Evidence on aging of reproductive **cells** and the relationship of cytomorphogenetic events to periodic rejuvenation of germ **cell** lines is summarized and evaluated here. Key events include the elimination or reversal of some DNA changes in germ **cells** through recombination and meiotic haploidization, cyclic regeneration of transcriptional and translational systems during gametogenesis and early development, and the selection of stable, viable genomes at various stages of the reproductive cycle. These rejuvenatory processes are compared and related to molecular events which **differentiated** somatic **cells** are unable to carry out.

1981

its biology. From this, it is clear that we have only begun to appreciate the biologic diversity, the geographic distribution, and the disease spectrum of this family of human T-lymphotropic retroviruses which we collectively term HTLV. At a basic level, HTLV provides a unique opportunity to study in vitro and in vivo mechanisms of **cell** transformation. Given its close association with adult T-**cell** leukemia and its ability to efficiently **immortalize** primary **cells** in vitro, we believe that HTLV will very likely harbor clues to the biology of **cell** growth, **differentiation** , and transformation. At a more clinical level, the close association between HTLV and a malignancy of clonally expanded (HTLV-containing) mature T-**cells** argues strongly for a causal relationship, although the mechanism for such is currently unknown. It is likely that further study of the molecular and **cellular** biology of this virus will bring together these basic and clinical findings and elucidate, at least in part, one mechanism for human leukemogenesis. From a more speculative viewpoint, the role of HTLV in the pathogenesis of human disease appears even broader. As discussed in this chapter, there are indications that all subtypes of HTLV may produce immunosuppression both in vitro and in vivo, and there is now exciting new data to suggest that a novel member of this family of viruses, HTLV-III, is causally linked to the AIDS syndrome. Moreover, the possibility has been raised that the immunosuppressive properties of HTLV could predispose patients to non-T-**cell** malignancies as occurs in patients with AIDS or chemically induced immunosuppression. Finally, by employing the experimental strategies which were successful in isolating HTLV-I, HTLV-II, and HTLV-III, it may be possible in the future to identify still other human retroviruses.

6/3,AB/67 (Item 67 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04454413 84140441 PMID: 6366382
Mechanisms for the initiation and promotion of carcinogenesis: a **review** and a new concept.
Scott R E; Wille J J; Wier M L
Mayo Clinic proceedings (UNITED STATES) Feb 1984, 59 (2) p107-17, ISSN 0025-6196 Journal Code: 0405543
Contract/Grant No.: CA-21722; CA; NCI; CA-28240; CA; NCI
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Carcinogenesis in humans is a multistage process, and the two major stages have been designated initiation and promotion. Although the biochemical basis for initiation and promotion remains to be established, recent research has provided important insights into potentially significant biologic mechanisms. These data are **reviewed**, and a new concept of carcinogenesis is presented. This concept suggests that the initiation of carcinogenesis may result from **cellular immortalization** and the development of defects in the integrated control of stem **cell** proliferation and **differentiation** and that the promotion of carcinogenesis may result when such initiated stem **cells** develop aberrant autoregulatory growth-control properties.

6/3,AB/68 (Item 68 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

03844408 82123757 PMID: 6173551
On the **immortality** of the germ line: genetic and biochemical mechanism. A **review**.
Medvedev Z A
Mechanisms of ageing and development (SWITZERLAND) Dec 1981, 17 (4)

p331-59, ISSN 0047-6374 Journal Code: 0347227
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The nature of the differences between mortal somatic **cells** and **immortal** germ **cell** lines constitutes a major area of theoretical gerontology which has not yet received adequate attention. Weismann's theory, first stated almost exactly a century ago, was recently reconsidered by Kirkwood and Holliday. They applied modern concepts and findings on the factors regulating the accuracy of synthesis of macromolecules to explain germ line **immortality** . In the present paper, evidence on ageing of reproductive **cells** and the relationship of cytomorphogenetic events to periodic rejuvenation of germ **cell** lines is summarized and evaluated. Key events include the elimination or reversal of some DNA changes in germ **cells** through recombination and meiotic haploidization, cyclic regeneration of transcriptional and translational systems during gametogenesis and early development, and the selection of stable, viable genomes at various stages of the reproductive cycle. These rejuvenatory processes are compared and related to molecular events which **differentiated** somatic **cells** are unable to carry out.

6/3,AB/69 (Item 69 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

03199015 80003226 PMID: 225148
The role of viral transformation and cytogenetic changes in viral oncogenesis.
Klein G
Ciba Foundation symposium (NETHERLANDS) Jun 27-29 1979, (66) p335-58, ISSN 0300-5208 Journal Code: 0356636
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A wide variety of DNA viruses and a more restricted family of RNA viruses can transform normal **cells** in vitro. Transformation means either **immortalization** and/or the appearance of certain phenotypic changes. Although it has been often inferred that in vitro transformation can be essentially equated with malignant transformation, increasing evidence indicates that the latter, reflected by tumorigenicity in vivo, requires additional cytogenetic changes. The evidence will be **reviewed** for EB virus-associated human malignancy (Burkitt's lymphoma) and the role of the 14q + translocation marker in human B-**cell** neoplasia. These findings point to an initiating role of viral transformation, reflected by in vitro **immortalization**, followed by a cytogenetic evolution where chromosome 14-associated changes are essential for the liberation of B lymphocytes from super-imposed controls. The contrast of tissue-associated, specific chromosomal changes that bring about malignant transformation after the initiating impact of **different** agents will be illustrated experimentally for murine T-**cell** lymphoma. Here, X-ray, DMBA and **different** virus (RadLV, Gross virus)-induced T lymphomas show the same chromosomal change: trisomy 15. It may be questioned whether viral transformation can ever lead to neoplasia in the absence of subsequent cytogenetic changes.

6/3,AB/70 (Item 70 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

03063467 79145794 PMID: 747780
The relationship between the spleen colony-forming **cell** and the